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(21) Application Number Tokuganhei 9-61875  (22) Application Date February 28, 1997	(71) Applicant 000005072 Banyu Pharmaceutical Co., Ltd. 2-3, Nihombashi Honcho 2-chome Chuo-ku, Tokyo (72) Inventor Katsuhisa KOJIRI c/o Banyu Pharmaceutical Co., Ltd. Tsukuba Research Institute 3, Okubo, Tsukuba-shi, Ibaraki (72) Inventor Hisao KONDO c/o Banyu Pharmaceutical Co., Ltd. Tsukuba Research Institute 3, Okubo, Tsukuba-shi, Ibaraki (72) Inventor Hiroharu ARAKAWA c/o Banyu Pharmaceutical Co., Ltd. Tsukuba Research Institute 3, Okubo, Tsukuba-shi, Ibaraki	
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(54) 【Title of Invention】 Antitumor Indolopyrrolocarbazole Derivatives

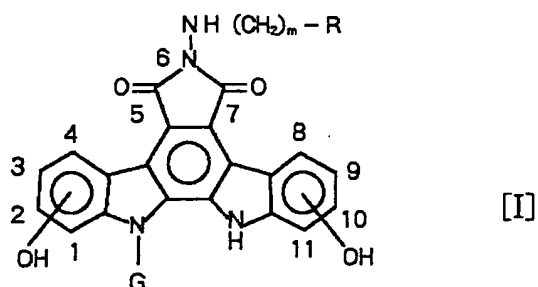
(57) 【Abstract】

【Problem】 Creation of Novel Antitumor Agents

【Solution Means】

- 5 A compound represented by the following general formula or a pharmaceutically acceptable salt thereof

【Com. 1】

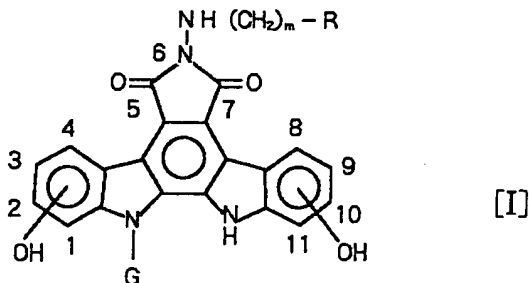


- wherein R represents a phenyl, naphthyl, pyridyl, furyl or thienyl group each of which has one or more substituents selected from the group consisting of a hydroxyl group, a lower alkoxy group, a hydroxy lower alkyl group and a hydroxy lower alkenyl group
- 5 except that when the phenyl, naphthyl, pyridyl, furyl or thienyl group has a lower alkoxy group as a substituent, each of which simultaneously has another substituent selected from the group consisting of a hydroxyl group, a lower alkoxy group, a hydroxy lower alkyl group and a hydroxy lower alkenyl group, m represents an integer of 1 to 3, and G represents a  $\beta$ -D-glucopyranosyl group, and the positions of
- 10 substitution of the hydroxyl groups on the indolopyrrolo[1,2-a]carbazole ring are the 1- and 11-positions, or the 2- and 10-positions.

【Scope of Claims】

【Claim 1】 A compound represented by the general formula or a pharmaceutically acceptable salt thereof

【Com. 1】



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wherein R represents a phenyl, naphthyl, pyridyl, furyl or thienyl group each of which has one or more substituents selected from the group consisting of a hydroxyl group, a lower alkoxy group, a hydroxy lower alkyl group and a hydroxy lower alkenyl group except that when the phenyl, naphthyl, pyridyl, furyl or thienyl group has a lower alkoxy group as a substituent, each of which simultaneously has another substituent selected from the group consisting of a hydroxyl group, a lower alkoxy group, a hydroxy lower alkyl group and a hydroxy lower alkenyl group,

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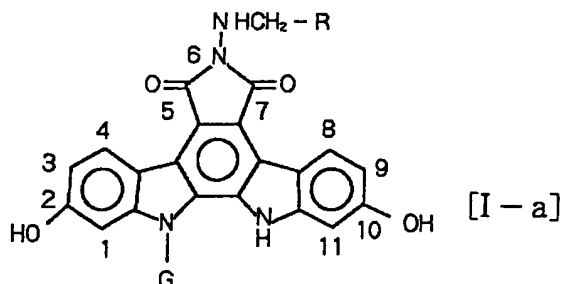
m represents an integer of 1 to 3, and

15

G represents a  $\beta$ -D-glucopyranosyl group, and the positions of substitution of the hydroxyl groups on the indolopyrrolocarbazole ring are the 1- and 11-positions, or the 2- and 10-positions.

【Claim 2】 The compound represented by the following general formula or the pharmaceutically acceptable salt thereof, according to claim 1

【Com. 2】

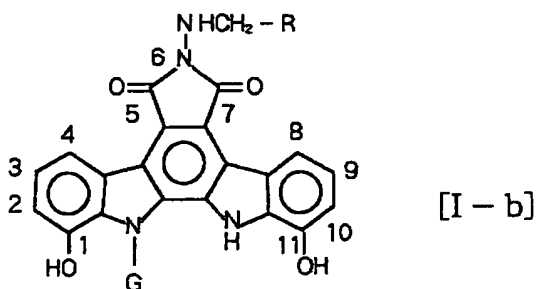


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wherein R, m and G are as defined in claim 1.

【Claim 3】 The compound represented by the following general formula or the pharmaceutically acceptable salt thereof, according to claim 1

【Com. 3】



wherein R, m and G are as defined in claim 1.

【Claim 4】 An antitumor agent containing a compound or pharmaceutically acceptable salt thereof according to claim 1,2 or 3.

#### 【Detailed Description of the Invention】

##### 【0001】

##### 【Industrially Applicable Field】

This invention is useful in the pharmaceutical field, and, more detailedly, relates to novel indolopyrrolocarbazole derivatives inhibiting growth of tumor cells and exerting antitumor effect, processes for preparation thereof and their use.

##### 【0002】

##### 【Prior Art】

Many compounds are already put to practical use as pharmaceuticals in the field of tumor chemotherapy. However, their effects are not always sufficient against various kinds of tumors, and the problem of resistance of tumor cells to these drugs also makes the methods of clinical use complicate (see, Proceedings of the 47th Annual Meeting of Japan Cancer Society, pages 12-15, 1988).

##### 【0003】

Under the circumstances, development of novel anticancer substances is always desired in the field of cancer treatment. Particularly, there is need for substances overcoming resistance to existing carcinostatic substances and showing effectiveness against cancers on which existing carcinostatic substances cannot exert sufficient effect.

##### 【0004】

Under these present circumstances, the present inventors have widely screened metabolites of microorganisms, and as a result, they found a novel compound BE-13793C (12,13-dihydro-1,11-dihydroxy-5H-indolo[2.3-a]pyrrolo[3,4-c]carbazole-5,7(6H)-dione) having antitumor activity (see, EP-A2-0388956).

##### 【0005】

Thereafter, they have tried to create compounds having further excellent antitumor activity by chemically modifying BE-13793C, and disclosed such compounds in prior patent applications (EP-A1-0528030, EP-A1-0545195, WO95/30682 and WO96/04293).

##### 【0006】

##### 【Problems to be Solved by the Invention】

It is a problem to be solved in the present invention to create compounds having further excellent antitumor activity by chemically modifying indolopyrrolocarbazole antitumor substances disclosed in the prior patent applications.

【0007】

【Means for Solving the Problems】

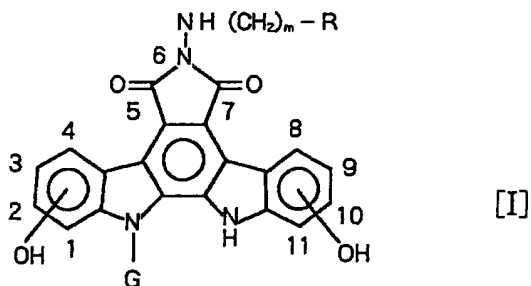
For solving the above problem, the present inventors have synthesized a wide range of indolopyrrolocarbazole derivatives and examined their antitumor activity, and found that compounds represented by the later-described general formula [I] show further excellent antitumor activity than the indolopyrrolocarbazole compounds disclosed in the prior applications, and completed the present invention.

【0008】

Namely, the invention relates to a compound represented by the general formula or a pharmaceutically acceptable salt thereof, and a use thereof:

【0009】

【Com. 4】



wherein R represents a phenyl, pyridyl, furyl or thienyl group each of which has one or more substituents selected from the group consisting of a hydroxyl group, a lower alkoxy group, a hydroxy lower alkyl group and a hydroxy lower alkenyl group except that when the phenyl, pyridyl, furyl or thienyl group has a lower alkoxy group as a substituent, each of which simultaneously has another substituent selected from the group consisting of a hydroxyl group, a lower alkoxy group, a hydroxy lower alkyl group and a hydroxy lower alkenyl group, m represents an integer of 1 to 3, and G represents a  $\beta$ -D-glucopyranosyl group, and the positions of substitution of the hydroxyl groups on the indolopyrrolocarbazole ring are the 1- and 11-positions, or the 2- and 10-positions.

【0010】

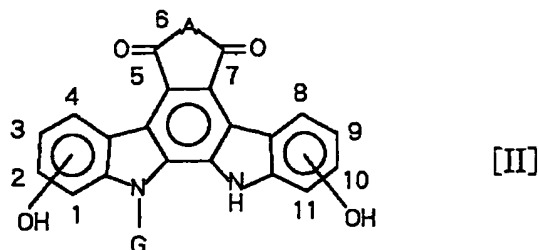
Description is made below on processes for preparing the compounds of the invention.

【0011】

An indolopyrrolocarbazole derivative of the invention can be prepared by reacting a compound represented by the general formula

【0012】

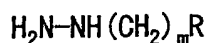
【Com. 5】



wherein, A represents NH or H, and G is as defined above,  
the compound being a known compound disclosed in EP-A1-0528030, EP-A1-0545195, WO95/30682 and WO96/04293, with a compound represented by the  
5 general formula

【0013】

【Com. 6】

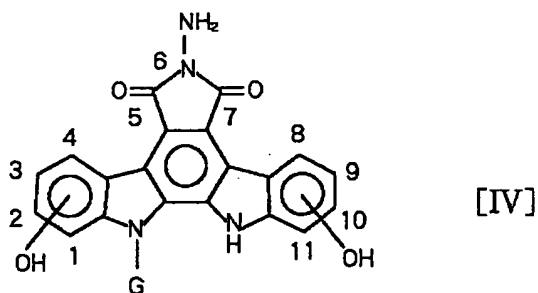


[III]

wherein, R and m are as defined above,  
or by condensing a compound represented by the general formula

【0014】

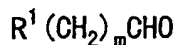
【Com. 7】



wherein, G is as defined above,  
with a compound represented by the general formula

【0015】

【Com. 8】



[V]

wherein,  $\text{R}^1$  has the same meaning as R or means R wherein hydroxyl groups are  
protected, and m is as defined above,

then carrying out reduction, and, if necessary, removing the protective groups,  
or by reacting a compound of the general formula [IV] with a compound represented  
by the general formula

【0016】

【Com. 9】



wherein, L means a leaving group, and  $R^1$  and m are as defined above,  
 5 , and, if necessary, removing the protective groups.

【0017】

The reaction between the compound represented by the general formula [II] and the compound represented by the general formula [III] is reaction between an imide or an acid anhydride and a hydrazine derivative, well-known in the chemical field. This  
 10 reaction can be carried out using a solvent usually having no bad influence on the reaction, such as, for example, tetrahydrofuran or N,N-dimethylformamide. The use amount of the compound [III] is usually a little excess to 5 molar equivalents based on the compound [II], but a largely excess use of the former is possible.

【0018】

15 The reaction temperature is usually in the range of  $-50^\circ\text{C}$  to the boiling point of the solvent, but, if necessary, temperature higher than or lower than the temperature can be used. The reaction time is usually in the range of 30 minutes to 2 days, but time longer than or shorter than the time can be used.

【0019】

20 The reaction of preparing a compound [I] by condensing a compound represented by the general formula [IV] with a compound represented by the general formula [V] and then carrying out reduction can be carried out in the same reaction system, but in some occasion, it is also possible to once isolate the Schiff base as an intermediate product. Namely usually, the reaction can be carried out by mixing the compound [IV] with the  
 25 compound [V] in a suitable solvent and then adding a reducing agent. The reaction is preferably carried out in the presence of an acid such as acetic acid or hydrochloric acid. As usable solvents, there can, for example, be mentioned alcoholic solvents such as methanol and ethanol, aprotic polar solvents such as N,N-dimethylformamide, etc. The reduction of the Schiff base can be carried out using a metal hydride complex such  
 30 as sodium cyanoborohydride, or the like, and also by catalytic reduction.

【0020】

The reaction between a compound of the general formula [IV] and a compound of the general formula [VI] is alkylation reaction of an amine, and can be carried out by a known method, for example by reaction with an alkyl halide, alkyl mesylate or alkyl  
 35 tosylate or the like.

【0021】

The products of the above reactions can be purified by methods known in the field of organic chemistry, for example by precipitation methods, solvent extraction methods, recrystallization, chromatography, etc.

40 【0022】

Further in the invention, pharmaceutically acceptable salts of compounds obtained by the above processes are included. As such salts, there can be mentioned salts with an alkali metal such as for example potassium or sodium, salts with an alkaline earth metal such as for example calcium, salts with a basic organic compound such as for  
 45 example ethylamine or arginine, salts with an inorganic acid such as hydrochloric acid or sulfuric acid, and salts with an organic acid such as acetic acid, citric acid or maleic acid.

5    **[0023]**

The compounds of the invention represented by the formula [I] show excellent antitumor action.

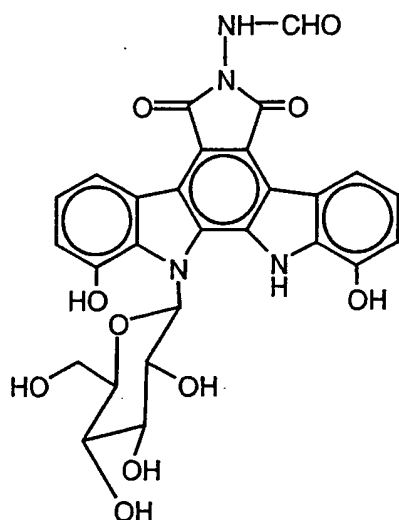
10    **[0024]**

5    Effect on human gastric cancer MX-1

MX-1 solid tumor previously subcutaneously implanted in a nude mouse and grown was thinly cut, and its cubes with each side 3 mm were subcutaneously implanted in test mice. After the implantation, starting from the time when the tumor grew into 0.3 cm<sup>3</sup>, various dosages of a test compound were injected once a day for 5 consecutive days into the tail veins of the mice. The same injections were then made for further 5 days after 2 days of interval (treatment schedule: 5/w×2) or once every 3-4 days, four times (treatment schedule: 2/w×2). 20 days or 32 days after the start of the treatment, the length (L) and the breadth (W) of each of the tumors were measured, and its volume (V) was calculated ( $V=1/2 \times L \times W^2$ ). A tumor growth inhibition proportion was calculated based on the volume, and a total dose to inhibit tumor growth by 75 % (GID<sub>75</sub>, mg/kg) was then determined. As a control compound, a compound represented by the following formula was used. The results are shown in Table 1.

15    **[0025]**

**[Com. 10]**



20    **[0026]**

**[Table 1]**

Table 1 Effect of Compounds of the Invention on human gastric cancer MX-1		
Test Compound	Treatment Schedule	GID <sub>75</sub> (mg/kg total)
Example 3	2/w×2	<90
Example 5	5/w×2	<90
Example 10	5/w×2	<90
Example 12	2/w×2	97
Example 14	2/w×2	<12
Example 27	2/w×2	<4.5
Example 28	2/w×2	<36
Example 30	5/w×2	16



Example 31	5/wx2	<30
Example 33	5/wx2	<30
Example 35	5/wx2	82
Example 36	5/wx2	<30
Example 37	5/wx2	32
Example 38	5/wx2	19
Example 39	2/wx2	<30
Control compound	5/wx2	1900

Compounds provided by the present invention show a much better antitumor action than the control compounds, as shown in the above pharmacological test results.

【0027】

As apparent from the results of the above pharmacological tests, the compounds of the invention show an excellent antitumor action, and are useful as antitumor agents for prophylaxis and/or treatment of diseases, especially for treatment of cancers. As administration forms in use as antitumor agents of the compounds of the invention, various forms can be selected, and there can be mentioned peroral agents such as for example tablets, capsules, powders, granules and liquids, or sterilized liquid parenteral agents such as for example solutions and suspensions.

【0028】

Solid preparations such as tablets, capsules, granules and powders can be prepared using compounds of the invention alone, but can also be prepared further using suitable additives. As the suitable additives, there can be mentioned conventional additives, for example, sugars such as for example lactose and glucose, starches such as for example corn, wheat and rice, fatty acids such as for example stearic acid, inorganic salts such as for example magnesium metasilicate aluminate and anhydrous calcium phosphate, synthetic macromolecules such as for example polyvinylpyrrolidone and polyalkylene glycols, fatty acid salts such as for example calcium stearate and magnesium stearate, alcohols such as for example stearyl alcohol and benzyl alcohol, synthetic cellulose derivatives such as for example methylcellulose, carboxymethylcellulose, ethylcellulose and hydroxypropylmethylcellulose, and further, water, gelatin, talc, vegetable oils, gum arabic, etc.

【0029】

These solid preparations such as tablets, capsules, granules and powders can contain, generally 0.1 to 100 % by weight, preferably 5 to 100 % by weight of an effective ingredient.

【0030】

Liquid preparations can be prepared as forms of suspensions, syrups, injections, etc. using suitable additives usually used in liquid preparations, such as water, alcohols or vegetable oils including soybean oil, peanut oil and sesame oil.

【0031】

Particularly, as solvents suitable in parenteral administration including intramuscular injection, intravenous injection and subcutaneous injection, there can for example be mentioned distilled water for injection, aqueous lidocaine hydrochloride solution (for intramuscular injection), physiological saline, aqueous glucose solution, ethanol, polyethylene glycol, liquids for intravenous injection (e.g., aqueous solutions of citric acid and sodium citrate, etc.), electrolyte solutions (for intravenous injection by drip

and for intravenous injection), etc., or their mixed solutions.

【0032】

These injections may include not only those wherein previous dissolution is made, but also those in the form of dissolving powder alone or with suitable additives when used. These injections usually contain 0.1 to 10 % by weight, preferably 1 to 5 % of an effective ingredient.

【0033】

Liquid preparations such as suspensions and syrups for oral administration can contain 0.5 to 10 % by weight of an effective ingredient.

【0034】

It should be noted that the actually preferred dose of the compounds of the invention is varied depending on kinds of compounds used, kinds of compositions prepared, application frequency, particular sites to be treated, hosts and tumors. For example, the dose of each compound per day and per one adult is 10 to 500 mg in the case of oral administration, and 10 to 100 mg in the case of parenteral administration, preferably intravenous injection. The frequency of administration is varied depending on administration methods and symptoms, but the administration can be made in a time or in divided 2 to 5 times. Administration methods including intermittent administration such as every two-days administration or every three-days administration can also be used.

【0035】

【Mode for Carrying out the Invention】

【0036】

【Example】

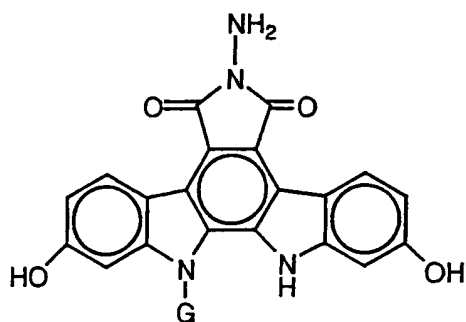
The invention is further specifically described below according to examples, but the invention is not limited to these examples.

【0037】

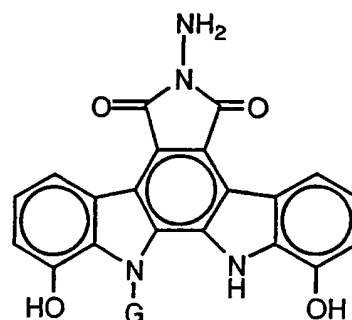
Compounds having the following structural formulae, which were used as starting compounds, are hereinafter referred to as follows.

【0038】

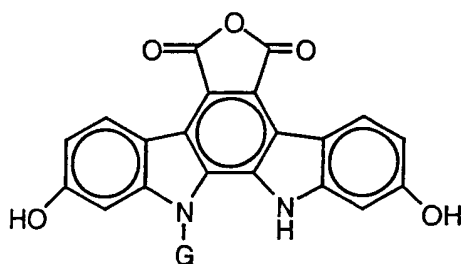
【Com. 11】



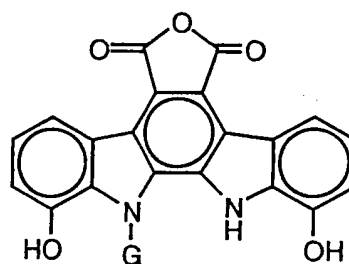
Compound A



Compound B



Compound C



Compound D

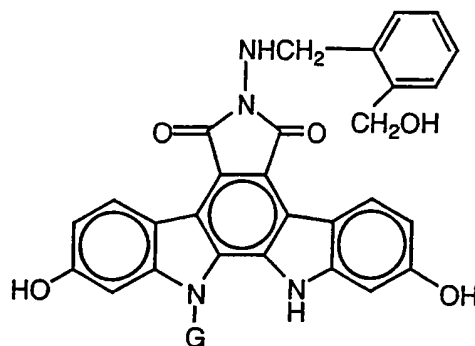
wherein, G represents a  $\beta$ -D-glucopyranosyl group, which is the same in the following examples.

#### 5 Example 1

Compound represented by the structural formula

[0039]

[Com. 12]



#### 10 [0040]

25 mg of Compound A and 90 mg of (2-t-butyldimethylsilyloxymethyl)benzyl bromide were dissolved in 1 ml of N,N-dimethylformamide, and the mixture was stirred overnight at room temperature. The resulting reaction mixture was concentrated to dryness, and the residue was placed on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated, and the concentrate was placed on a Sephadex LH-20 column for

chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness, and the residue was washed with chloroform to obtain 3.6 mg of the compound represented by the above formula.

FAB-MS(m/z):655(M+H)<sup>+</sup>

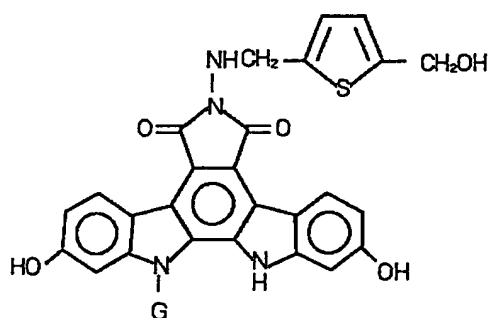
<sup>1</sup>H-NMR(300MHz,DMSO-d<sub>6</sub>,δp p m)11.19(1H,s),9.78(1H,s),9.75(1H,s),8.86(1H,d,J=8.6Hz),8.78(1H,d,J=8.2Hz),7.44(1H,d,J=7.2Hz),7.37(1H,d,J=7.6Hz),7.13-7.28(3H,m),6.98(1H,s),6.78-6.88(2H,m),5.95-6.05(2H,m),5.85(1H,br),5.33(1H,d,J=3.2Hz),5.10-5.17(2H,m),4.92(1H,d,J=4.0Hz),4.28(2H,d,J=5.2Hz),3.72-4.10(4H,m),3.45-3.55(2H,m)

### Example 2

Compound represented by the structural formula

[0041]

[Com. 13]



30 mg of Compound A and 30 mg of (5-t-butyltrimethylsilyloxymethylthiophene)-2-carboxyaldehyde were dissolved in 6 ml of methanol, 30 ml of acetic acid was added, and the mixture was stirred at 80°C for 4 hours. The reaction mixture was cooled to room temperature, 20 mg of sodium cyanoborohydride and 200 ml of a 10 % solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was concentrated to dryness under reduced pressure, and the residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 27 mg of the compound represented by the above formula.

R<sub>f</sub> value: 0.37 (Kieselgel 60F<sub>254</sub> made by Merck Co., developing solvent; acetonitrile: tetrahydrofuran: toluene: water: acetic acid = 4:2:2:0.5:0.1)

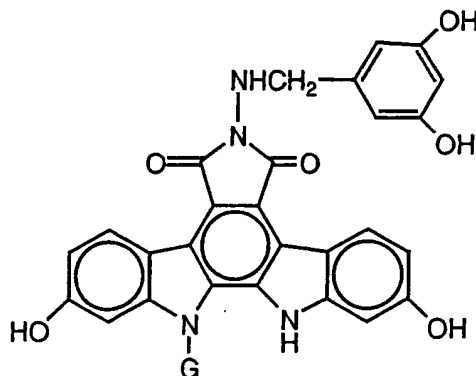
FAB-MS(m/z):660(M<sup>+</sup>)

<sup>1</sup>H-NMR(300MHz,DMSO-d<sub>6</sub>,δp p m):11.19(1H,s),9.79(1H,s),9.75(1H,s),8.86(1H,d,J=9.3Hz),8.78(1H,d,J=9.0Hz),7.17(1H,d,J=2.1Hz),6.97(1H,d,J=2.1Hz),6.89(1H,d,J=3.6Hz),6.82(1H,dd,J=2.1,9.3Hz),6.79(1H,dd,J=2.1,9.0Hz),6.73(1H,d,J=3.3Hz),6.10(1H,t,J=4.5Hz),5.97(1H,d,J=8.1Hz),5.86(1H,t,J=3.3Hz),5.35(1H,t,J=6.0Hz),5.32(1H,d,J=4.8Hz),5.12(1H,d,J=4.8Hz),4.92(1H,d,J=5.4Hz),4.52(2H,d,J=5.7Hz),4.40(2H,d,J=4.2Hz),4.02(1H,m),3.91(2H,m),3.78(1H,m),3.50(2H,m)

### Example 3

Compound represented by the structural formula

[0042]  
[Com. 14]



100 mg of Compound A and 131.2 mg of 3,5-dihydroxybenzaldehyde were dissolved  
5 in 10 ml of N,N-dimethylformamide, and the mixture was stirred at 80°C for 48 hours.  
The reaction mixture was concentrated under reduced pressure, and the residue was  
placed on a Sephadex LH-20 column for chromatography and eluted with methanol.  
Fractions containing the desired compound were concentrated to dryness to obtain 90.3  
10 mg of an intermediate compound. 20 mg of this intermediate compound was  
suspended in 5 ml of methanol, 10 mg of sodium cyanoborohydride and several drops  
of a 10% solution of hydrochloric acid in methanol were added, and the mixture was  
stirred at room temperature for 30 minutes. After distilling off methanol under reduced  
pressure, water was added to the mixture, and the mixture was extracted with ethyl  
15 acetate. The organic layer was washed with saturated saline, dried and concentrated,  
and the residue was placed on a Sephadex LH-20 column for chromatography and  
eluted with methanol. Fractions containing the desired compound were concentrated to  
dryness to obtain 18 mg of the compound represented by the above formula.

R<sub>f</sub> value: 0.30 (Kieselgel 60F<sub>254</sub> made by Merck Co., developing solvent ;  
acetonitrile:tetrahydrofuran:toluene:water:acetic acid=4:2:2:0.5:0.1)

20 FAB-MS(m/z):657(M+H)<sup>+</sup>

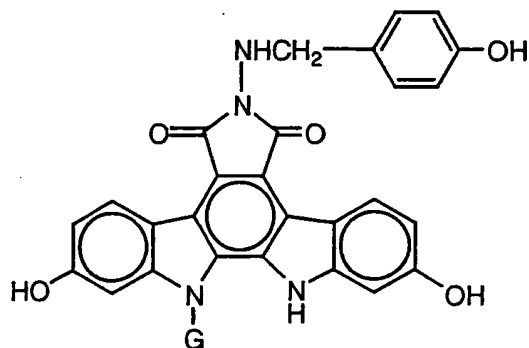
<sup>1</sup>H-NMR(300MHz,DMSO-d<sub>6</sub>,δp pm)11.19(1H,s),9.77(2H,br),9.11(2H,s),8.87(1H,d,  
J=8.6Hz),8.79(1H,d,J=8.6Hz),7.17(1H,s),6.97(1H,s),6.78-6.84(2H,m),6.34(2H,s),  
6.06(1H,s),5.96(1H,d,J=8.3Hz),5.83-5.87(2H,m),5.34(1H,s),5.12(1H,s),  
4.92(1H,d,J=3.9Hz),4.04(2H,d,J=4.5Hz),3.91-3.99(3H,m),3.75-3.88(1H,m),3.49(2H,s)

25

Example 4

Compound represented by the structural formula

[0043]  
[Com. 15]



30 mg of Compound A and 14 mg of 4-hydroxybenzaldehyde were dissolved in 6 ml of methanol, 14 ml of acetic acid was added, and the mixture was stirred at 80°C for 2 hours. The reaction mixture was cooled to room temperature, 20 mg of sodium cyanoborohydride and 200 ml of a 10% solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was placed on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 31 mg of the compound represented by the above formula.

R<sub>f</sub> value: 0.41 (Kieselgel 60F<sub>254</sub> made by Merck Co., developing solvent ; acetonitrile:tetrahydrofuran:toluene:water:acetic acid=4:2:2:0.5:0.1)

FAB-MS(m/z):640(M<sup>+</sup>)

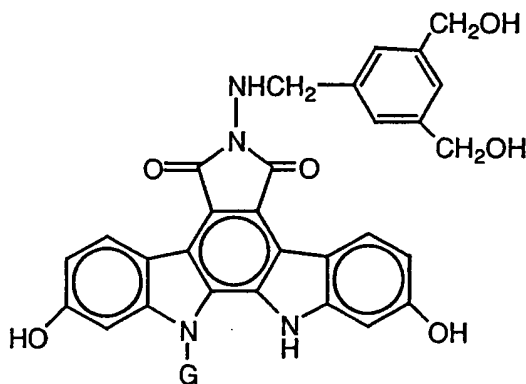
<sup>1</sup>H-NMR(300MHz,DMSO-d<sub>6</sub>,δp pm)11.17(1H,s),9.77(1H,s),9.74(1H,s),9.24(1H,s), 8.86(1H,d,J=8.4Hz),8.78(1H,d,J=8.4Hz),7.25(2H,d,J=8.7Hz),7.17(1H,d,J=1.8Hz),6.97 (1H,d,J=1.8Hz),6.83(1H,dd,J=1.8,8.7Hz),6.80(1H,dd,J=1.8,8.7Hz),6.67(2H,d,J=8.1Hz ),5.96(1H,d,J=8.1Hz),5.87(1H,t,J=4.8Hz),5.85(1H,t,J=3.9Hz),5.32(1H,d,J=4.5Hz),5.10 (1H,d,J=5.1Hz),4.91(1H,d,J=4.8Hz),4.12(2H,m),4.03(1H,m),3.91(2H,s),3.78(1H,m),3. 50(2H,m)

## Example 5

Compound represented by the structural formula

【0044】

【Com. 16】



30 mg of Compound A and 20 mg of 3,5-dihydroxymethylbenzaldehyde were dissolved in 6 ml of methanol, 20 ml of acetic acid was added, and the mixture was stirred at 80°C for 3 hours. The reaction mixture was brought back to room temperature, 10 mg of sodium cyanoborohydride and several drops of a 10% solution of hydrochloric acid in methanol were added, and the mixture was stirred at room

temperature for 30 minutes. The reaction mixture was placed on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 22 mg of the compound represented by the above formula.

- 5 R<sub>f</sub> value: 0.35 (Kieselgel 60F<sub>254</sub> made by Merck Co., developing solvent ; acetonitrile:tetrahydrofuran:toluene:water:acetic acid=4:2:2:0.5:0.1)

FAB-MS(m/z):684 (M<sup>+</sup>)

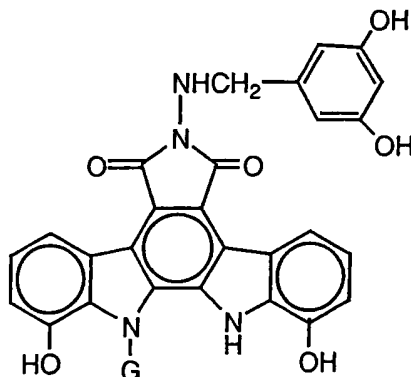
- 10 <sup>1</sup>H-NMR(300MHz,DMSO-d<sub>6</sub>,δp p m)11.19(1H,s),9.79(1H,s),9.76(1H,s),8.88(1H,d, J=8.7Hz),8.80(1H,d,J=8.7Hz),7.32(2H,s),7.18(2H,s),6.98(1H,d,J=1.8Hz),6.81(2H,dt,J=1.8,8.7Hz),5.97(1H,d,J=8.7Hz),5.93(1H,t,J=4.8Hz),5.87(1H,t,J=3.2Hz),5.34(1H,d,J=4.2Hz),5.15(2H,t,J=6.3Hz),5.12(1H,d,J=4.8Hz),4.92(1H,d,J=4.8Hz),4.49(2H,s),4.47(2H,s),4.22(2H,d,J=5.1Hz),4.03(1H,m),3.92(2H,s),3.78(1H,m),3.50(2H,m)

#### Example 6

- 15 Compound represented by the structural formula

[0045]

[Com. 17]



- 20 53 mg of Compound B and 69 mg of 3,5-dihydroxybenzaldehyde were dissolved in 3 ml of N,N-dimethylformamide, and the mixture was stirred overnight at 80°C. The reaction mixture was concentrated under reduced pressure, the concentrate was dissolved in 10 ml of methanol, an excess amount of sodium cyanoborohydride and 0.5 ml of a 10% solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure, water was added, the mixture was extracted with a mixed solvent of ethyl acetate/methyl ethyl ketone, and the organic layer was washed with saturated saline, dried and concentrated. The residue was placed on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 4.8 mg of the compound represented by the above formula.

R<sub>f</sub> value: 0.2 (Kieselgel 60F<sub>254</sub> made by Merck Co., developing solvent ; chloroform:methanol=3:1)

FAB-MS(m/z):657(M+H)<sup>+</sup>

- 35 <sup>1</sup>H-NMR(300MHz,DMSO-d<sub>6</sub>,δp p m)10.89(1H,s),10.33(1H,br),9.97(1H,br),9.11(1H,s),8.70(1H,d,J=6.8Hz),8.52(1H,d,J=7.7Hz),7.15-7.21(2H,m),6.98-7.06(3H,m),6.36(2H,d,J=1.9Hz),6.06(1H,s),5.91(1H,t,J=5.4Hz),5.41(1H,d,J=5.6Hz),5.30-5.45(1H,m),

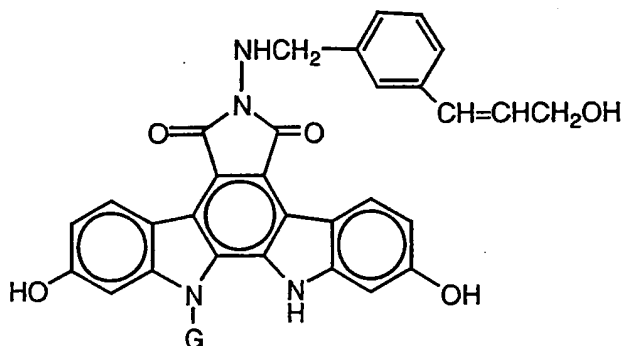
5.20(1H,d,J=4.6Hz),4.87(1H,m),3.94-4.10(4H,m),3.56-3.77(3H,m),3.38-3.43(2H,m)

#### Example 7

Compound represented by the structural formula

5    【0046】

      【Com. 18】



30 mg of Compound C and 30 mg of 3-(3-hydroxypropenyl)benzylhyrazine trifluoroacetate salt were dissolved in 2 ml of N,N-dimethylformamide, several drops of triethylamine was added, and the mixture was stirred overnight at 80°C. The reaction mixture was concentrated to dryness, and the residue was purified by preparative thin layer chromatography (developing solvent ; acetonitrile:tetrahydrofuran:toluene:water:acetic acid=4:2:2:0.5:0.1) to obtain 8.2 mg of the compound represented by the above formula.

15 Rf value: 0.51 (Kieselgel 60F<sub>254</sub> made by Merck Co., developing solvent ; acetonitrile:tetrahydrofuran:toluene:water:acetic acid=4:2:2:0.5:0.1)

FAB-MS(m/z):

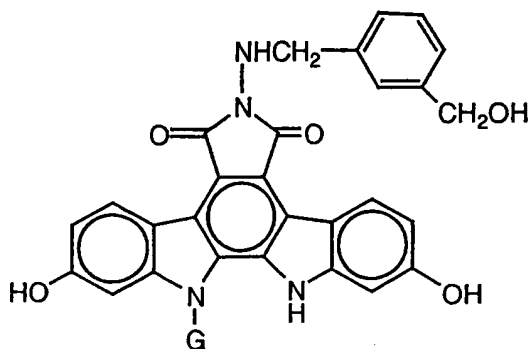
<sup>1</sup>H-NMR (300MHz,DMSO-d<sub>6</sub>,δp p m) 11.18(1H,s),9.50-10.00(2H,br),8.86(1H,d,J=8.1Hz),8.78(1H,d,J=8.5Hz),7.59(1H,s),7.20-7.40(3H,m),7.16(1H,s),6.97(1H,s),6.73-6.89(2H,m),6.42(1H,d,J=3.6Hz),6.31-6.48(1H,m),6.10(1H,t,J=4.0Hz),5.95(1H,d,J=7.9Hz),5.88(1H,br),5.36(1H,br),5.13(1H,br),4.91(1H,br),4.84(1H,br),4.26(2H,s),4.09(2H,s),3.70-4.10(4H,m),3.41-3.58(2H,m)

#### Example 8

Compound represented by the structural formula

25    【0047】

      【Com. 19】



45.5 mg of Compound C and 67.2 mg of 3-hydroxymethylbenzylhyrazine trifluoroacetate salt were dissolved in 3 ml of N,N-dimethylformamide, several drops



of aqueous saturated sodium bicarbonate solution was added, and the mixture was stirred overnight at 70°C. The reaction mixture was diluted with methyl ethyl ketone, washed successively with dilute hydrochloric acid, water and saturated saline, dried and concentrated. The residue was roughly purified by preparative thin layer chromatography (developing solvent ; acetonitrile:tetrahydrofuran:toluene:water:acetic acid=4:2:2:0.5:0.1), placed on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 1.6 mg of the compound represented by the above formula.

Rf value: 0.40(Kieselgel 60F<sub>254</sub> made by Merck Co., developing solvent ; acetonitrile:tetrahydrofuran:toluene:water:acetic acid=4:2:2:0.5:0.1)

FAB-MS(m/z): 654 (M<sup>+</sup>)

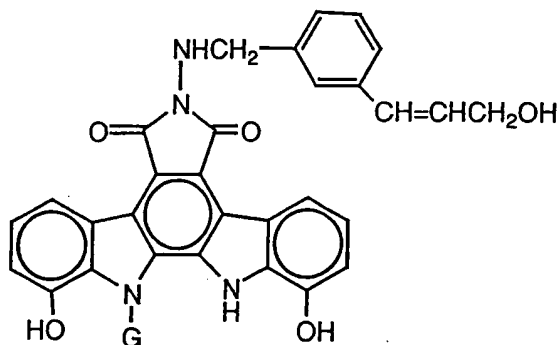
<sup>1</sup>H-NMR(300MHz,DMSO-d<sub>6</sub>,δp pm)11.18(1H,s),8.86(1H,d,J=8.4Hz),8.78(1H,d,J=8.7Hz),7.42(1H,s),7.40(1H,d,J=7.5Hz),7.27(1H,t,J=7.2Hz),7.18(1H,d,J=7.5Hz),7.17(1H,s),6.98(1H,d,J=1.8Hz),6.81(2H,dt,J=1.8,8.1Hz),6.00(2H,dt,J=1.5,4.8Hz),5.95(1H,d,J=8.7Hz),5.43(1H,br),5.16(2H,br),4.93(1H,br),4.47(2H,s),4.25(1H,d,J=4.8Hz),4.10(1H,br),4.02(1H,d,J=10.8Hz),3.90(2H,m),3.76(1H,m)

#### Example 9

Compound represented by the structural formula

[0048]

[Com. 20]



30 mg of Compound D and 40 mg of 3-(3-hydroxypropenyl)benzylhydrazone trifluoroacetate salt were dissolved in 1 ml of N,N-dimethylformamide, 0.5 ml of triethylamine was added, and the mixture was stirred at 80°C for 1.5 hours. The reaction mixture was diluted with a mixed solvent of ethyl acetate/methyl ethyl ketone, washed successively with dilute hydrochloric acid and saturated saline, dried and concentrated. The residue was placed on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated, and the concentrate was placed again on a Sephadex LH-20 column for chromatography and eluted with ethanol. Fractions containing the desired compound were concentrated to dryness to obtain 7.8 mg of the compound represented by the above formula.

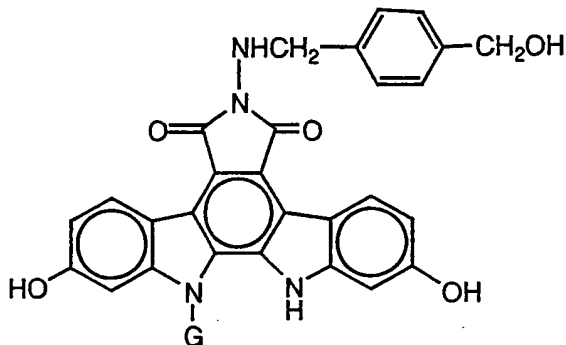
Rf value: 0.48 (Kieselgel 60F<sub>254</sub> made by Merck Co., developing solvent ; acetonitrile:tetrahydrofuran:toluene:water:acetic acid=4:2:2:0.5:0.1)

<sup>1</sup>H-NMR(300MHz,DMSO-d<sub>6</sub>,δp pm)10.89(1H,s),10.35(1H,br),9.95(1H,br),8.70(1H,d,J=7.8Hz),8.52(1H,d,J=7.8Hz),7.60(1H,s),6.91-7.40(8H,m),6.53(1H,d,J=16.2Hz),6.39(1H,td,J=4.6,16.2Hz),6.16(1H,t,J=5.6Hz),5.41(1H,d,J=5.6Hz),5.35(1H,br),5.20(1

H,d,J=4.9Hz),4.86(1H,t,J=3.6Hz),4.84(1H,t,J=5.6Hz),4.28(2H,s),3.89-4.12(4H,m),  
3.30-3.78(4H,m)

#### Example 10

- 5 Compound represented by the structural formula  
 【0049】  
 【Com. 21】



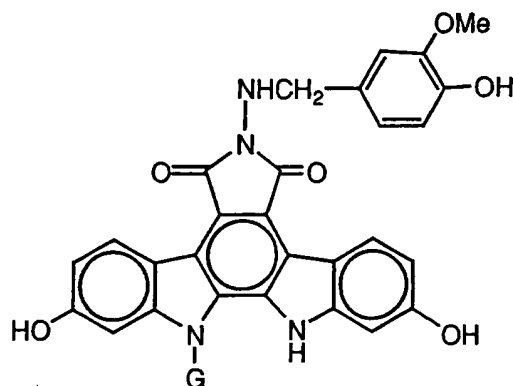
- 10 100 mg of Compound C and 100 mg of 4-hydroxymethylbenzylhyrazine  
 hydrochloride were dissolved in 5 ml of N,N-dimethylformamide, 0.5 ml of aqueous  
 saturated sodium bicarbonate solution was added, and the mixture was stirred at room  
 temperature for 1 hour and then at 80°C for 30 minutes. The reaction mixture was  
 diluted with methyl ethyl ketone, washed successively with 2N hydrochloric acid and  
 15 saturated saline, dried and concentrated. The residue was placed on a Sephadex LH-20  
 column for chromatography and eluted with methanol. Fractions containing the desired  
 compound were concentrated to dryness to obtain 33 mg of the compound represented  
 by the above formula.

R<sub>f</sub> value: 0.47 (Kieselgel 60F<sub>254</sub> made by Merck Co., developing solvent ;  
 chloroform:methanol:tetrahydrofuran=2:1:1)

- 20 FAB-MS (m/z): 655 (M+H)<sup>+</sup>  
<sup>1</sup>H-NMR (300MHz,DMSO-d<sub>6</sub>,δp p m) 11.10(1H,br),8.83(1H,d,J=9.3Hz),8.73(1H,d,  
 J=8.4Hz),7.44(2H,d,J=8.4Hz),7.23(2H,d,J=7.8Hz),7.11(1H,s),6.94(1H,s),6.78(2H,dt,J  
 =9.0,2.1Hz),6.02(1H,t,J=4.8Hz),5.92(1H,d,J=8.1Hz),4.80-5.23(2H,br),4.43(2H,s),  
 4.24(2H,s),4.03(1H,m),3.90(2H,m),3.77(1H,m),3.50(2H,m),3.25-3.42(3H,m)

#### Example 11

Compound represented by the structural formula  
 【0050】  
 【Com. 22】



52 mg of Compound C and 61.4 mg of 3-methoxy-4-hydroxybenzylhydrazine hydrochloride were dissolved in 2 ml of N,N-dimethylformamide, 0.5 ml of aqueous saturated sodium bicarbonate solution was added, and the mixture was stirred at 80°C for 1 hour. The reaction mixture was concentrated to dryness, and the residue was placed on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 20 mg of the compound represented by the above formula.

Rf value: 0.33 (Kieselgel 60F<sub>254</sub> made by Merck Co., developing solvent ; chloroform:methanol:tetrahydrofuran=3:1:1)

FAB-MS (m/z): 655 (M+H)<sup>+</sup>

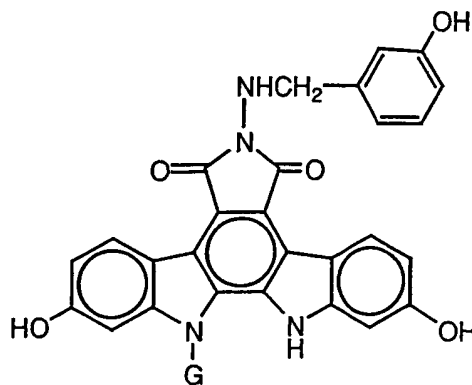
<sup>1</sup>H-NMR (300MHz,DMSO-d<sub>6</sub>,δp pm) 11.12(1H,s), 9.77(1H,s), 8.74(1H,s), 8.86(1H,s), 8.78(1H,d,J=8.6Hz), 8.76(1H,s), 7.16(2H,d,J=8.1Hz), 6.97(1H,s), 6.70-6.85(3H,m), 6.64(1H,d,J=8.5Hz), 5.86-6.04(2H,m), 5.85(1H,t,J=3.6Hz), 5.32(1H,d,J=3.9Hz), 5.10(1H,d,J=4.2Hz), 4.90(1H,d,J=4.3Hz), 4.11-4.21(2H,m), 3.86-4.10(4H,m), 3.77(3H,m), 3.35-3.52(2H,m)

#### Example 12

Compound represented by the structural formula

【0051】

【Com.23】



40 mg of Compound C and 31 mg of 3-hydroxybenzylhydrazine hydrochloride were dissolved in 2 ml of N,N-dimethylformamide, 0.5 ml of aqueous saturated sodium bicarbonate solution was added, and the mixture was stirred overnight at 80°C. The reaction mixture was diluted with ethyl acetate, washed successively with 2N hydrochloric acid, aqueous saturated sodium bicarbonate solution and saturated saline, dried and concentrated. The residue was placed on a Sephadex LH-20 column for

chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 17.2 mg of the compound represented by the above formula.

R<sub>f</sub> value: 0.24 (Kieselgel 60F<sub>254</sub> made by Merck Co., developing solvent; acetonitrile:tetrahydrofuran:toluene:water:acetic acid=4:2:2:0.5:0.1)

FAB-MS (m/z): 641 (M+H)<sup>+</sup>

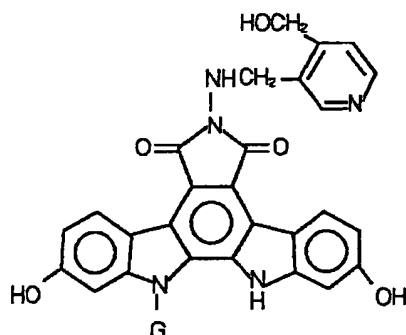
<sup>1</sup>H-NMR (300MHz, DMSO-d<sub>6</sub>, δp pm) 11.18(1H, s), 9.76(1H, s), 9.73(1H, s), 9.28(1H, s), 8.87(1H, d, J=8.5Hz), 8.79(1H, d, J=9.0Hz), 7.17(1H, s), 7.18(1H, dd, J=7.5, 8.0Hz), 6.97(1H, d, J=2.3Hz), 6.78-6.93(4H, m), 6.60(1H, dd, J=1.5, 8.0Hz), 5.96(2H, m), 5.85(1H, m), 5.30(1H, d, J=4.2Hz), 5.09(1H, d, J=4.9Hz), 4.90(1H, d, J=5.1Hz), 4.15(2H, s), 3.72-4.05(4H, m), 3.50(2H, m)

### Example 13

Compound represented by the structural formula

[0052]

[Com. 24]



43 mg of Compound A and 100 mg of (3-*t*-butyldimethylsilyloxymethyl)-3-pyridinecarbaldehyde were suspended in 10 ml of methanol, 18 ml of acetic acid was added, and the mixture was stirred overnight at 80°C. The reaction mixture was concentrated, put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness, and the residue was dissolved in 5 ml of a mixed solvent of methanol/tetrahydrofuran (1:1). 5 % palladium-carbon was added and the mixture was stirred at room temperature for 3.5 hours under a hydrogen stream. The reaction mixture was filtered using Celite and the residue was dissolved in 5 ml of tetrahydrofuran. An excess amount of tetrabutylammonium fluoride (1.0 M tetrahydrofuran solution) was added and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was concentrated, put on a Sephadex LH-20 column for chromatography, and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 4.3 mg of the compound represented by the above formula.

R<sub>f</sub> value: 0.1 (Kieselgel 60F<sub>254</sub> made by Merck Co., developing solvent; acetonitrile:tetrahydrofuran:toluene:water:acetic acid = 4:2:2:0.5:0.1)

FAB-MS(m/z):656(M+H)<sup>+</sup>

<sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>, δp pm):11.18(1H, s), 9.75(1H, s), 9.73(1H, s), 8.84(1H, d,

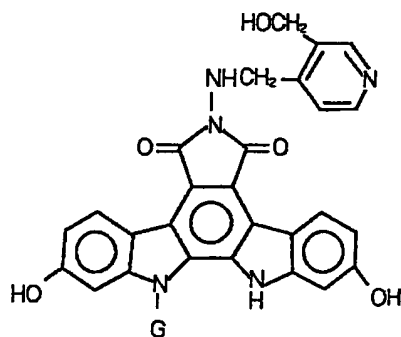
J=8.4Hz), 8.77(1H, d, J=8.9Hz), 8.42(1H, d, J=4.9Hz), 8.39(1H, s), 7.48(1H, d, J=4.9Hz), 7.17(1H, d, J=1.1Hz), 6.97(1H, s), 6.78-6.83(2H, m), 6.09(1H, t, J=4.7Hz), 5.97(1H, d, J=6.6Hz), 5.84(1H, t, J=3.8Hz), 5.39(1H, t, J=5.8Hz), 5.30(1H, d, J=4.8Hz), 5.09(1H, d, J=4.2Hz), 4.95(2H, d, J=5.3Hz), 4.90(1H, d, J=3.3Hz), 4.27(2H, d, J=4.2Hz), 3.75-4.03(4H, m), 3.47-3.52(2H, m)

#### Example 14

Compound represented by the structural formula

[0053]

[Com. 25]



98 mg of Compound A and 92.1 mg of 4-(3-t-butoxymethyl)pyridinecarbaldehyde were dissolved in 5 ml of methanol, 18 ml of acetic acid was added, and the mixture was stirred overnight at 80°C. The reaction mixture was concentrated, and the resulting crystals were washed with chloroform and dissolved in a mixed solvent of methanol/tetrahydrofuran (1:1). 5 % palladium-carbon was added and the mixture was stirred for 3 hours under a hydrogen stream. The reaction mixture was filtered using Celite and the filtrate was concentrated. The residue was dissolved in tetrahydrofuran, tetrabutylammonium fluoride was added, and the mixture was stirred at room temperature for 30 minutes. Water was added, the mixture was extracted with methyl ethyl ketone, and the organic layer was washed with an aqueous saturated sodium chloride solution and concentrated. The concentrate was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 13.5 mg of the compound represented by the above formula.

R<sub>f</sub> value: 0.10 (Kieselgel 60F<sub>254</sub> made by Merck Co., developing solvent; chloroform: methanol: tetrahydrofuran = 2:2:1)

FAB-MS(m/z): 656(M+H)<sup>+</sup>

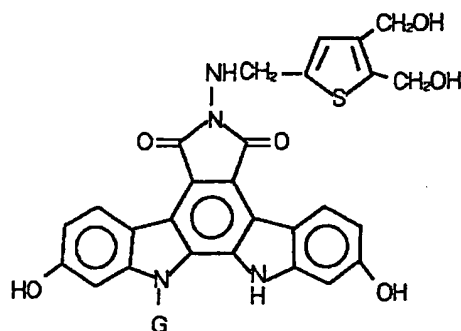
<sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>, δp pm): 11.19(1H, s), 9.78(1H, s), 9.75(1H, s), 8.85(1H, d, J=9.1Hz), 8.77(1H, d, J=9.1Hz), 8.51(1H, s), 8.11(1H, d, J=5.1Hz), 7.59(1H, d, J=4.6Hz), 7.17(1H, d, J=2.1Hz), 6.97(1H, d, J=1.8Hz), 6.79-6.85(2H, m), 6.25(1H, t, J=5.0Hz), 5.98(1H, d, J=8.3Hz), 5.86(1H, d, J=4.5Hz), 5.32(1H, d, J=4.5Hz), 5.23(1H, t, J=5.6Hz), 5.11(1H, d, J=4.4Hz), 4.91(1H, d, J=4.9Hz), 4.74(2H, d, J=5.2Hz), 4.35(2H, d, J=7.8Hz), 3.73-4.05(4H, m), 3.43-3.52(2H, m)

## Example 15

Compound represented by the structural formula

【0054】

【Com. 26】



50 mg of Compound A and 100 mg of (4,5-t-butyldimethylsilyloxymethyl) thiophene-2-carboxyaldehyde were suspended in 10 ml of anhydrous methanol, 100 ml of acetic acid was added, and the mixture was stirred at 80°C for 2 hours. The reaction mixture was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 40 mg of an intermediate compound. This was suspended in 3 ml of methanol, 12 mg of sodium cyanoborohydride and 300 ml of a 10 % solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness, and the residue was purified by preparative thin layer chromatography (Kieselgel 60F<sub>254</sub> made by Merck Co., developing solvent; acetonitrile: tetrahydrofuran: toluene: water: acetic acid = 4:2:2:0.5:0.1) to obtain 26 mg of the compound represented by the above formula.

R<sub>f</sub> value: 0.28 (Kieselgel 60F<sub>254</sub> made by Merck Co., developing solvent; acetonitrile: tetrahydrofuran: toluene: water: acetic acid = 4:2:2:0.5:0.1)

FAB-MS(m/z):690(M<sup>+</sup>)

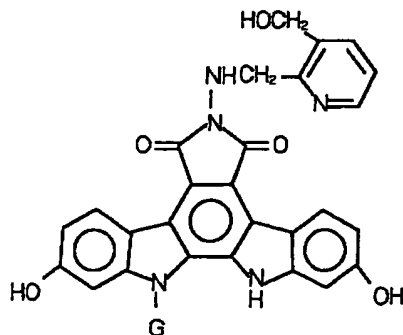
<sup>1</sup>H-NMR(300MHz,DMSO-d<sub>6</sub>,δppm):11.17(1H,s),9.50-10.15(2H,br),8.86(1H,d,J=8.4Hz),8.78(1H,d,J=8.7Hz),7.16(1H,d,J=1.8Hz),6.97(1H,d,J=2.1Hz),6.92(1H,s),6.82(1H,dd,J=1.8,8.7Hz),6.79(1H,dd,J=2.1,8.4Hz),6.04(1H,t,J=5.1Hz),6.04(1H,t,J=5.1Hz),5.96(1H,d,J=8.1Hz),5.88(1H,br),5.35(1H,br),5.28(1H,br),5.15(1H,br),4.93(2H,br),4.53(2H,br),4.73(2H,d,J=4.5Hz),4.30(1H,s),4.00(1H,m),3.91(2H,m),3.77(1H,m),3.52(2H,m)

## Example 16

Compound represented by the structural formula

【0055】

【Com. 27】



30 mg of Compound A and 50 mg of 2-(3-t-butyldimethylsilyloxymethyl) pyridinecarbaldehyde were suspended in 6 ml of methanol, 30 ml of acetic acid was added, and the mixture was stirred at 80°C for 2 hours. The reaction mixture was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to obtain 40 mg of an intermediate compound. This was dissolved in a mixed solvent of tetrahydrofuran/methanol (2:1), 15 mg of sodium cyanoborohydride and 3 ml of a solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 3 hour. The reaction mixture was concentrated, put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 27 mg of the compound represented by the above formula.

Rf value: 0.12 (Kieselgel 60F<sub>254</sub> made by Merck Co., developing solvent; acetonitrile: tetrahydrofuran: toluene: water: acetic acid = 4:2:2:0.5:0.1)

FAB-MS(m/z):656(M+H)<sup>+</sup>

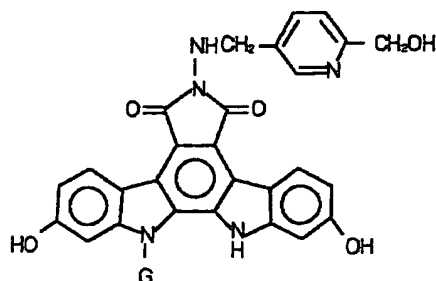
<sup>1</sup>H-NMR(300MHz,DMSO-d<sub>6</sub>,δp pm):11.18(1H,br),9.77(2H,br),8.82(1H,d, J=9.0Hz), 8.784(1H,d,J=9.0Hz),8.27(1H,dd,J=1.8,5.1Hz),7.83(1H,d,J=8.1Hz),7.28(1H,dd,J=8.1, 5.1Hz),7.17(1H,d,J=1.8Hz),6.98(1H,d,J=1.8Hz),6.82(1H,dd,J=1.8,9.1Hz),6.79(1H,dd, J=1.8,9.0Hz),6.15(1H,t,J=5.1Hz),5.97(1H,d,J=8.1Hz),5.86(1H,t,J=4.2Hz),5.33(1H,d,J =5.4Hz),5.31(1H,d,J=5.4Hz),5.12(1H,d,J=4.8Hz),4.93(1H,d,J=4.5Hz),4.87(2H,d,J=6.0 Hz),4.36(2H,d,J=5.1Hz),4.03(1H,m),3.91(2H,s),3.79(1H,m),3.51(2H,m)

#### Example 17

Compound represented by the structural formula

【0056】

【Com. 28】



30 mg of Compound C and 65 mg of (6-hydroxymethyl-3-pyridylmethyl)hydrazine hydrochloride were dissolved in 5 ml of N,N-dimethylformamide, 0.5 ml of triethylamine was added, and the mixture was stirred at 80°C for 3 hours. 33 mg of (6-hydroxymethyl-3-pyridylmethyl)hydrazine hydrochloride was added and the mixture was stirred at 80°C for 2 hours. The reaction mixture was concentrated to dryness, and the residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated, and the residue was again put on a Sephadex LH-20 column for chromatography and eluted with ethanol. Fractions containing the desired compound were concentrated to dryness to obtain 7.2 mg of the compound represented by the above formula.

FAB-MS(m/z):656(M+H)<sup>+</sup>

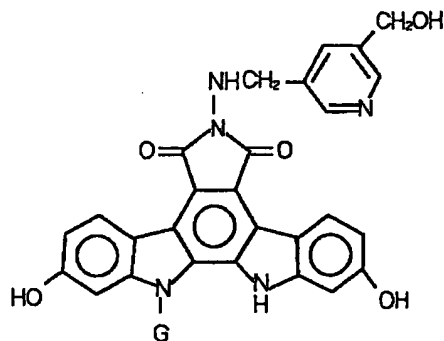
<sup>1</sup>H-NMR(300MHz,DMSO-d<sub>6</sub>,δp pm):11.12(1H,br),8.81(1H,d,J=8.7Hz),8.73(1H,d,J=8.7Hz),8.51(1H,s),7.90(1H,d,J=7.9Hz),7.39(1H,d,J=7.9Hz),7.11(1H,s),6.93(1H,s),6.77(2H,t,J=8.7Hz),6.21(1H,t,J=3.8Hz),5.92(1H,d,J=7.9Hz),4.85-5.50(5H,br),4.48(2H,s),4.27(2H,d,J=3.8Hz),3.70-4.05(4H,m),3.45-3.52(2H,m)

#### Example 18

Compound represented by the structural formula

【0057】

【Com. 29】



12.5 mg of Compound C and 42 mg of (5-hydroxymethyl-3-pyridylmethyl) hydrazine hydrochloride were dissolved in 1 ml of N,N-dimethylformamide, 0.1 ml of triethylamine was added, and the mixture was stirred at 80°C for 2.5 hours. 0.1 ml of triethylamine was added and the mixture was stirred overnight at 50°C. The reaction mixture was concentrated to dryness, and the residue was put on a Sephadex LH-20



column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated, and the residue was again put on a Sephadex LH-20 column for chromatography and eluted with ethanol. Fractions containing the desired compound were concentrated to dryness to obtain 2.4 mg of the compound represented by the above formula.

R<sub>f</sub> value: 0.18 (Kieselgel 60F<sub>254</sub> made by Merck Co., developing solvent; acetonitrile: tetrahydrofuran: toluene: water: acetic acid = 4:2:2:0.5:0.1)

FAB-MS(m/z):656(M+H)<sup>+</sup>

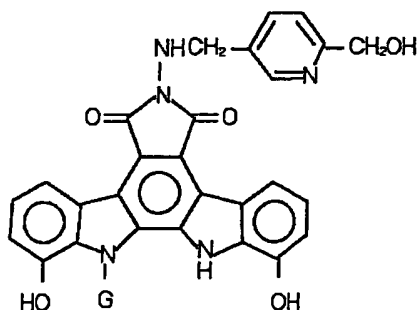
<sup>1</sup>H-NMR(300MHz,DMSO-d<sub>6</sub>,δ<sub>p</sub> ppm):11.18(1H,br),9.60-10.02(2H,br),8.84(1H,d,J=8.5Hz),8.76(1H,d,J=8.6Hz),8.55(1H,s),8.37(1H,s),7.84(1H,s),7.16(1H,s),7.00(1H,s),6.75-6.85(2H,m),6.21(1H,t,J=4.7Hz),5.95(1H,d,J=7.8Hz),5.88-5.95(1H,br),5.40-5.48(1H,br),5.26-5.35(1H,br),5.15-5.25(1H,br),4.90-4.93(1H,br),4.56(2H,d,J=4.7Hz),4.50(2H,s),3.72-4.05(4H,m),3.45-3.55(2H,m)

#### Example 19

Compound represented by the structural formula

[0058]

[Com. 30]



30 mg of Compound D and 65 mg of (6-hydroxymethyl-3-pyridylmethyl)hydrazine hydrochloride were dissolved in 5 ml of N,N-dimethylformamide, 0.5 ml of triethylamine was added, and the mixture was stirred at 80°C for 1.5 hours. The reaction mixture was dried and concentrated, and the residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 29 mg of the compound represented by the above formula.

FAB-MS(m/z):656(M+H)<sup>+</sup>

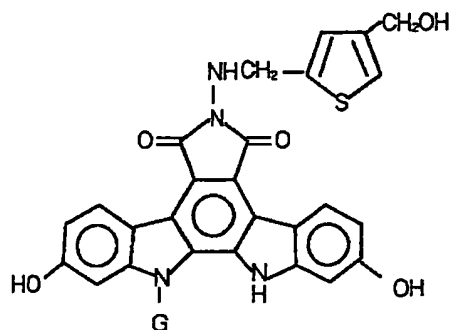
<sup>1</sup>H-NMR(300MHz,DMSO-d<sub>6</sub>,δ<sub>p</sub> ppm):10.89(1H,br),10.36(1H,br),9.97(1H,br),8.67(1H,d,J=7.9Hz),8.52(1H,d,J=2.2Hz),8.50(1H,d,J=7.9Hz),7.93(1H,dd,J=2.2,8.1Hz),7.41(1H,d,J=8.1Hz),7.18(2H,t,J=7.9Hz),7.02(1H,d,J=7.9Hz),7.00(2H,t,J=7.9Hz),6.29(1H,t,J=4.5Hz),5.42(1H,d,J=5.6Hz),5.33(1H,d,J=6.1Hz),5.32(1H,t,J=6.0Hz),5.21(1H,d,J=5.3Hz),4.82-4.91(1H,br),4.48(2H,d,J=6.0Hz),4.29(2H,d,J=4.5Hz),3.91-4.12(2H,m),3.52-3.79(3H,m),3.30-3.40(1H,m)

#### Example 20

Compound represented by the structural formula

【0059】

【Com. 31】



- 5 30 mg of Compound B and 152 mg of 4-(t-butyldimethylsilyloxyethyl)thiophene-2-carbaldehyde were suspended in 6 ml of anhydrous methanol, 30 ml of acetic acid was added, and the mixture was stirred at 80°C for 2 hours. The reaction mixture was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 31 mg of an
- 10 intermediate compound. This was suspended in 3 ml of methanol, 30 mg of sodium cyanoborohydride and 300 ml of a 10 % solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was diluted with ethyl acetate, washed with water and an aqueous saturated sodium chloride solution, dried and concentrated. The residue was put on a Sephadex
- 15 LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 5 mg of the compound represented by the above formula.

Rf value: 0.43 (made by Merck Co., toluene: water: acetic acid = 4:2:2:0.5:0.1)

FAB-MS(m/z):675(M)<sup>+</sup>

- 20 <sup>1</sup>H-NMR(300MHz,DMSO-d<sub>6</sub>,δp pm):11.19(1H,s),9.80(2H,br),8.86(1H,d,J=9.0Hz),8.78(1H,d,J=8.7Hz),7.17(1H,d,J=1.8Hz),7.03(1H,s),6.98(1H,d,J=2.1Hz),6.95(1H,s),6.80(2H,dt,J=2.1,8.7Hz),6.08(1H,t,J=5.1Hz),5.96(1H,d,J=7.8Hz),5.89(1H,br),5.36(1H,br),5.13(1H,br),4.93(1H,br),4.57(1H,br),4.38(2H,d,J=4.2Hz),4.05(2H,m),3.92(2H,s),3.77(1H,m),3.50(5H,m)

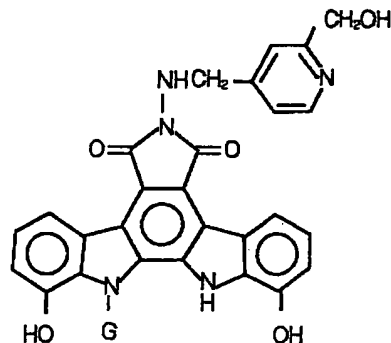
25

#### Example 21

Compound represented by the structural formula

【0060】

【Com. 32】



17 mg of Compound D and 12 mg of 4-(2-hydroxymethyl-4-pyridylmethyl) hydrazine trifluoroacetate were dissolved in 2 ml of N,N-dimethylformamide, 0.1 ml of triethylamine was added, and the mixture was stirred at 75°C for 2 hours. Water and ethyl acetate were added to the reaction mixture, and the mixture was extracted three times with water. Sodium chloride was added to the aqueous layer and the mixture was extracted three times with methyl ethyl ketone. The organic layer was dried and concentrated, and the residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 8 mg of the compound represented by the above formula.

FAB-MS(m/z):656(M+H)<sup>+</sup>

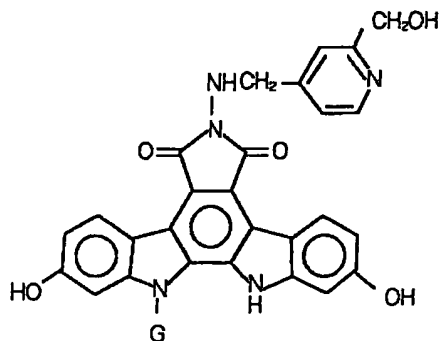
<sup>1</sup>H-NMR(300MHz,DMSO-d<sub>6</sub>,δp pm):10.90(1H,br),8.66(1H,d,J=7.6Hz),8.50(1H,d,J=7.6Hz),8.41(1H,d,J=5.0Hz),7.57(1H,s),7.48(1H,d,J=5.0Hz),7.17(2H,t,J=7.6Hz),7.07(1H,d,J=7.6Hz),7.00(1H,d,J=7.6Hz),6.98(1H,t,J=7.6Hz),6.32(1H,t,J=4.8Hz),5.36(1H,t,J=3.7Hz),5.10-5.50(4H,br),4.51(2H,d,J=3.7Hz),4.34(2H,d,J=4.8Hz),3.91-4.12(2H,m), 3.51-3.80(3H,m)

#### Example 22

Compound represented by the structural formula

[0061]

[Com. 33]



17 mg of Compound C and 12 mg of (2-hydroxymethyl-4-pyridylmethyl)hydrazine

trifluoroacetate were dissolved in 1 ml of N,N-dimethylformamide, 0.1 ml of triethylamine was added, and the mixture was stirred at 80°C for 3.5 hours. Water and ethyl acetate were added to the reaction mixture, and the mixture was separated into two layers. Sodium chloride was added to the aqueous layer and the mixture was extracted with methyl ethyl ketone. The organic layer was dried and concentrated, and the residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 4 mg of the compound represented by the above formula.

FAB-MS(m/z):656(M+H<sup>+</sup>)

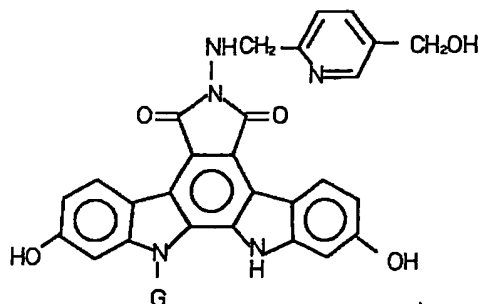
<sup>1</sup>H-NMR(300MHz,DMSO-d<sub>6</sub>,δp pm):11.17(1H,br),9.55-10.05(2H,br),8.85(1H,d,J=8.4Hz),8.77(1H,d,J=8.2Hz),8.41(1H,d,J=5.1Hz),7.56(1H,s),7.47(1H,d,J=5.1Hz),7.15(1H,s),6.96(1H,s),6.72-6.85(2H,m),6.26(1H,t,J=4.9Hz),5.94(1H,d,J=8.6Hz),5.80-5.99(1H,br),5.30-5.42(2H,br),5.10-5.20(1H,br),4.85-4.95(1H,br),4.51(2H,d,J=1.8Hz),4.32(2H,d,J=4.5Hz),3.89-4.04(1H,m),3.90(2H,m),3.74-3.78(1H,m),3.50 (2H,m)

#### Example 23

Compound represented by the structural formula

[0062]

[Com. 34]



14 mg of Compound A and 14.7 mg of 5-t-butyldimethylsilyloxymethylpyridine-2-carbaldehyde were suspended in 2 ml of anhydrous methanol, 8 ml of acetic acid was added, and the mixture was stirred overnight at 80°C. The reaction mixture was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 15.3 mg of an intermediate compound. 75 mg of sodium cyanoborohydride was suspended in 1 ml of tetrahydrofuran, and 0.55 ml of zinc chloride (1.0 M diethyl ether solution) was added dropwise. A suspension of 15.3 mg of the intermediate compound in 3 ml of tetrahydrofuran was added, and the mixture was stirred at room temperature for 2.5 hours. An aqueous saturated sodium bicarbonate solution was added to the reaction mixture, and the mixture was extracted with methyl ethyl ketone. The organic layer was dried and concentrated, the residue was dissolved in 3 ml of tetrahydrofuran, and an excess amount of tetrabutylammonium fluoride (1 M tetrahydrofuran solution) was added dropwise at 0°C. The mixture was stirred at room temperature for 30 minutes, water was added, and the mixture was extracted with methyl ethyl ketone. The organic layer was dried and concentrated, and the residue was put on a Sephadex LH-20

column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 4.5 mg of the compound represented by the above formula.

Rf value: 0.1 (Kieselgel 60F<sub>254</sub> made by Merck Co., developing solvent; chloroform: methanol: tetrahydrofuran = 3:1:1)

FAB-MS(m/z):656(M+H)<sup>+</sup>

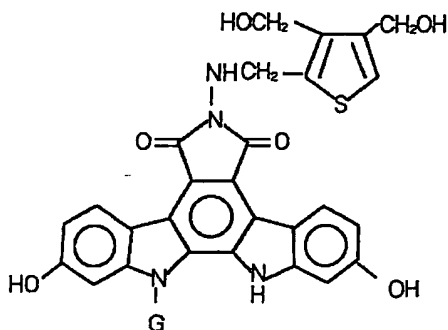
<sup>1</sup>H-NMR(300MHz,DMSO-d<sub>6</sub>,δp pm):11.18(1H,s),9.77(2H,br),8.84(1H,d,J=8.5Hz), 8.76(1H,d,J=8.6Hz),8.35(1H,d,J=1.7Hz),7.72(2H,s),7.17(1H,d,J=1.7Hz),6.98(1H,d,J= 1.9Hz),6.78-6.98(2H,m),6.22(1H,t,J=4.6Hz),5.96(1H,d,J=8.9Hz),5.87(1H,br),5.35(1H, br),5.22(1H,t,J=2.0Hz),5.11(1H,br),4.91(1H,br),4.46(2H,d,J=4.2Hz),4.35(2H,d,J=4.6H z),3.73-4.09(4H,m),3.49(2H, s)

#### Example 24

Compound represented by the structural formula

[0063]

[Com. 35]



30 mg of Compound A and 30 mg of 3,4-bis-(t-butyldimethylsilyloxymethyl) thiophene-2-carbaldehyde were suspended in 6 ml of anhydrous methanol, 30 ml of acetic acid was added, and the mixture was stirred at 80°C for 2 hours. The reaction mixture was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 31 mg of an intermediate compound. This was suspended in 5 ml of methanol, 10 mg of sodium cyanoborohydride and 100 ml of a 10 % solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was diluted with ethyl acetate, and washed with water and an aqueous saturated sodium chloride solution. The organic layer was dried and concentrated, and the residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 25 mg of the compound represented by the above formula.

Rf value: 0.30 (Kieselgel 60F<sub>254</sub> made by Merck Co., developing solvent; acetonitrile: tetrahydrofuran: toluene: water: acetic acid = 4:2:2:0.5:0.1)

FAB-MS(m/z):691(M+H)<sup>+</sup>

<sup>1</sup>H-NMR(300MHz,DMSO-d<sub>6</sub>,δp pm):11.19(1H,s),9.79(1H,s),9.76(1H,s),8.86(1H,

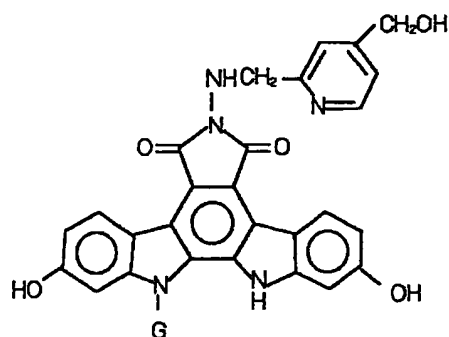
d,J=8.4Hz),8.78(1H,d,J=8.7Hz),7.18(1H,d,J=1.8Hz),7.15(1H,s),6.98(1H,d,J=2.1Hz),6.82(2H,dt,J=8.7,1.8Hz),6.04(1H,t,J=5.4Hz),5.97(1H,d,J=8.1Hz),5.86(1H,t,J=3.6Hz),5.33(1H,d,J=4.2Hz),5.12(1H,d,J=4.2Hz),5.01(1H,t,J=6.0Hz),4.93(1H,d,J=4.8Hz),4.85(1H,t,J=5.7Hz),4.52(2H,d,J=5.7Hz),4.70(2H,d,J=5.7Hz),4.40(2H,d,J=4.8Hz),4.01(1H,m),3.92(2H,m),3.77(1H,m),3.50(2H,m)

#### Example 25

Compound represented by the structural formula

【0064】

【Com. 36】



18 mg of Compound A and 7 mg of 4-hydroxymethylpyridine-2-carbaldehyde were suspended in 2 ml of anhydrous methanol, several drops of acetic acid were added, and the mixture was stirred at 80°C for 1.5 hours. The reaction mixture was concentrated to dryness, and the residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 22 mg of an intermediate compound. 90 mg of sodium cyanoborohydride was suspended in 1 ml of tetrahydrofuran, and 0.66 ml of zinc chloride (1.0 M diethyl ether solution) was added dropwise. A suspension of 22 mg of the intermediate compound in 3 ml of tetrahydrofuran was added, and the mixture was stirred at room temperature for 2.5 hours. Water was added to the reaction mixture, and the mixture was made weakly alkaline with an aqueous saturated sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was dried and concentrated, and the residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 11 mg of the compound represented by the above formula.

FAB-MS(m/z):656(M+H)<sup>+</sup>

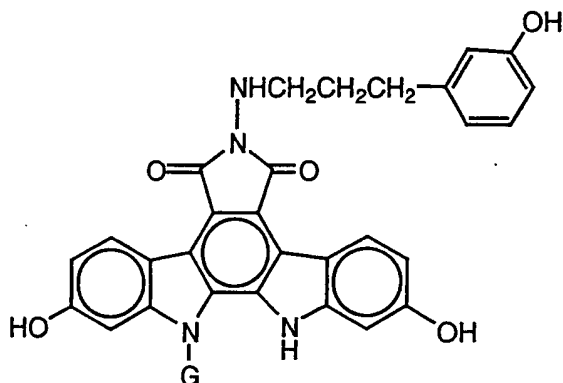
<sup>1</sup>H-NMR(300MHz,DMSO-d<sub>6</sub>,δp pm):11.21(1H,s),9.80(1H,s),9.77(1H,s),8.86(1H,d,J=8.6Hz),8.78(1H,d,J=8.1Hz),7.82-7.95(1H,m),7.68-7.75(1H,m),7.33-7.43(1H,m),7.19(1H,s),7.00(1H,s),6.78-6.89(2H,m),6.22(1H,t,J=4.5Hz),5.97(1H,d,J=7.9Hz),5.86(1H,t,J=3.8Hz),5.33(1H,d,J=4.2Hz),5.29(1H,t,J=5.9Hz),5.11(1H,d,J=5.0Hz),4.91(1H,d,J=4.1Hz),4.42(2H,d,J=5.5Hz),4.33(2H,d,J=1.6Hz),3.99-4.09(1H,m),3.91(2H,m),3.72-3.80(1H,m),3.50(2H,m)

#### Example 26

Compound represented by the structural formula

【0065】

【Com. 37】



- 5 20 mg of Compound A and 20 mg of 3-(3-t-butyldimethylsilyloxyphenyl)propanal were suspended in 4 ml of anhydrous methanol, 20 ml of acetic acid was added, and the mixture was stirred at 80°C for 8 hours. The reaction mixture was concentrated, and the concentrate was placed on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 14 mg of an intermediate compound. This was suspended in 5 ml of methanol, 7.5 mg of sodium cyanoborohydride and 0.5 ml of a 10 % solution of hydrochloric acid in methanol were added, the mixture was stirred at room temperature for 2 hours, 0.5 ml of 2N hydrochloric acid was added, and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate, washed successively with water and saturated saline. The organic layer was dried and concentrated, and the residue was placed on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 12 mg of the compound represented by the above formula.

- 20 R<sub>f</sub> value: 0.36 (Kieselgel 60F<sub>254</sub> made by Merck Co., developing solvent; acetonitrile:tetrahydrofuran:toluene:water:acetic acid=4:2:2:0.5:0.1)

FAB-MS (m/z): 669 (M+H)<sup>+</sup>

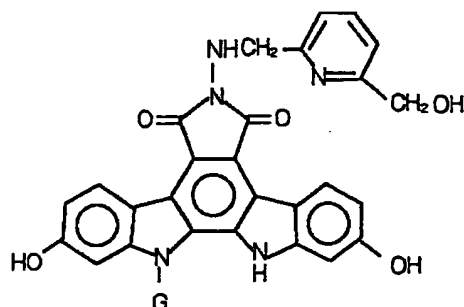
- <sup>1</sup>H-NMR (300MHz,DMSO-d<sub>6</sub>,δp pm) 11.18(1H,s), 9.65(3H,br), 8.87(1H,d,J=8.1Hz), 8.79(1H,d,J=8.1Hz), 7.17(1H,d,J=1.7Hz), 7.02(1H,t,J=8.1Hz), 6.98(1H,d,J=1.7Hz), 6.81(2H,dt,J=1.7,5.7Hz), 6.64(1H,d,J=8.1Hz), 6.62(1H,s), 6.57(1H,dd,J=1.8,8.1Hz), 5.96(1H, d,J=8.1Hz), 5.87(1H,br), 5.74(1H,t,J=4.8Hz), 5.35(1H,br), 5.12(1H,br), 4.92(1H,br), 4.02(1H,d,J=10.8Hz), 3.91(2H,m), 3.79(1H,d,J=9.9Hz), 3.51(2H,d,J=7.5Hz), 3.02(2H,m), 2.65(2H,t,J=7.2Hz), 1.72(2H,t,J=8.1Hz)

- 30 Example 27

Compound represented by the structural formula

【0066】

【Com. 38】



15 mg of Compound A and 6.9 mg of 6-hydroxymethylpyridine-2-carbaldehyde were suspended in 1 ml of anhydrous methanol, several drops of acetic acid were added, and the mixture was stirred at 80°C for 5 hours. The reaction mixture was concentrated to dryness, and the residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 5.2 mg of an intermediate compound. 68 mg of sodium cyanoborohydride was suspended in 2 ml of tetrahydrofuran, and 0.5 ml of zinc chloride (1.0 M diethyl ether solution) was added dropwise. A suspension of 5.2 mg of the intermediate compound in 1 ml of tetrahydrofuran was added, and the mixture was stirred overnight at room temperature. Water was added to the reaction mixture, and the mixture was made weakly alkaline with an aqueous saturated sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was dried and concentrated, and the residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 2.0 mg of the compound represented by the above formula.

Rf value: 0.29 (Kieselgel 60F<sub>254</sub> made by Merck Co., developing solvent: acetonitrile: tetrahydrofuran: toluene: water: acetic acid = 4:2:2:0.5:0.1)

FAB-MS(m/z):656(M+H<sup>+</sup>)

<sup>1</sup>H-NMR(300MHz,DMSO-d<sub>6</sub>,δp pm):11.21(1H,s),9.80(1H,s),9.77(1H,s),8.86(1H,d, J=8.6Hz),8.78(1H,d,J=8.1Hz),7.82-7.95(1H,m),7.68-7.75(1H,m),7.33-7.43(1H,m), 7.19(1H,s),7.00(1H,s),6.78-6.89(2H,m),6.22(1H,t,J=4.5Hz),5.97(1H,d,J=7.9Hz),5.86 (1H,t,J=3.8Hz),5.33(1H,d,J=4.2Hz),5.29(1H,t,J=5.9Hz),5.11(1H,d,J=5.0Hz),4.91(1H,d ,J=4.1Hz),4.42(2H,d,J=5.5Hz),4.33(2H,d,J=1.6Hz),3.99-4.09(1H,m),3.91(2H,m),3.72-3.80(1H,m),3.50(2H,m)

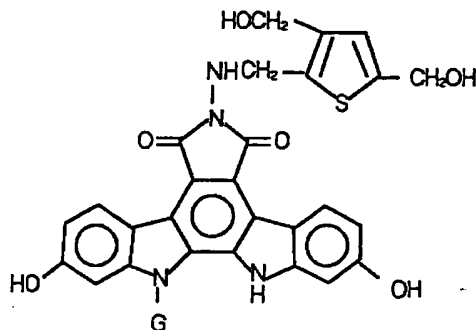
#### Example 28

Compound represented by the structural formula

【0067】

【Com. 39】





40 mg of Compound A and 60 mg of 3,5-bis-(t-butyltrimethylsilyloxymethyl) thiophene-2-carbaldehyde were suspended in 8 ml of anhydrous methanol, 40 ml of acetic acid was added, and the mixture was stirred at 80°C for 2 hours. The reaction mixture was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 46 mg of an intermediate compound. This was suspended in 5 ml of methanol, 30 mg of sodium cyanoborohydride and 300 ml of a 10 % solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was diluted with ethyl acetate, and washed with water and an aqueous saturated sodium chloride solution. The organic layer was dried and concentrated, and the residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 36 mg of the compound represented by the above formula.

Rf value: 0.24 (Kieselgel 60F<sub>254</sub> made by Merck Co., developing solvent: acetonitrile: tetrahydrofuran: toluene: water: acetic acid = 4:2:2:0.5:0.1)

FAB-MS(m/z):690(M)<sup>+</sup>

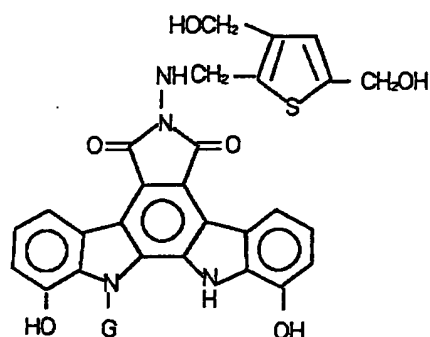
<sup>1</sup>H-NMR(300MHz,DMSO-d<sub>6</sub>,δp p m):11.19(1H,s),9.79(1H,s),9.76(1H,s),8.86(1H,d, J=8.4Hz),8.78(1H,d,J=8.4Hz),7.18(1H,d,J=1.8Hz),6.98(1H,d,J=1.8Hz),6.83(1H,s),6.82(2H,dt,J=1.8,8.4Hz),5.99(1H,t,J=4.8Hz),5.97(1H,d,J=9.0Hz),5.87(1H,t,J=4.2Hz),5.35(1H,t,J=5.4Hz),5.33(1H,d,J=4.8Hz),5.12(1H,d,J=5.1Hz),4.96(1H,d,J=5.7Hz),4.94(1H,d,J=5.4Hz),4.49(4H,t,J=6.6Hz),4.34(2H,d,J=4.8Hz),4.03(1H,m),3.92(2H,m),3.77(1H,m),3.50(2H,m)

#### Example 29

Compound represented by the structural formula

【0068】

【Com. 40】



50 mg of Compound B and 60 mg of 3,5-bis-(t-butyldimethylsilyloxymethyl) thiophene-2-carbaldehyde were dissolved in 12 ml of anhydrous methanol/*N,N*-dimethylformamide (5:1), 50 ml of acetic acid was added, and the mixture was stirred overnight at 80°C. The reaction mixture was diluted with ethyl acetate, washed with water and an aqueous saturated sodium chloride solution, dried, and concentrated. The residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness, and the residue was dissolved in 6 ml of a mixed solvent of tetrahydrofuran/methanol (2:1). 30 mg of sodium cyanoborohydride and 300 ml of a 10 % solution of hydrochloric acid in methanol were added, and the mixture was at room temperature for 1 hour. The reaction mixture was diluted with ethyl acetate, and washed with an aqueous saturated sodium bicarbonate solution and an aqueous saturated sodium chloride solution. The organic layer was dried and concentrated, and the residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 37 mg of the compound represented by the above formula.

Rf value: 0.31 (Kieselgel 60F<sub>254</sub> made by Merck Co., developing solvent: acetonitrile: tetrahydrofuran: toluene: water: acetic acid = 4:2:2:0.5:0.1)

FAB-MS(*m/z*): 690(M)<sup>+</sup>

<sup>1</sup>H-NMR(300MHz,DMSO-

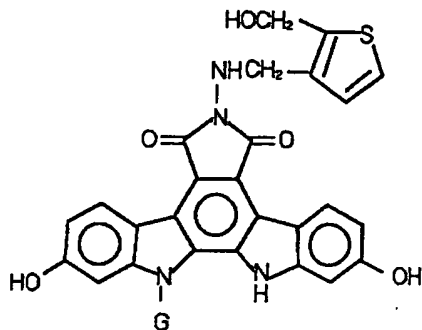
*d*<sub>6</sub>, δ ppm): 10.90(1H,s), 10.37(1H,br), 9.98(1H,br), 8.69(1H, d, *J*=8.4Hz), 8.52(1H,d,*J*=8.4Hz), 7.19(2H,dt,*J*=1.5,8.4Hz), 7.05(1H,d,*J*=8.6Hz), 7.01(2H, t, *J*=8.4Hz), 6.83(1H,s), 6.04(1H,t,*J*=4.8Hz), 5.42(1H,d,*J*=5.7Hz), 5.35(2H,t,*J*=6.0Hz), 5.21(1H,d,*J*=5.4Hz), 4.95(1H,t,*J*=6.0Hz), 4.91(1H,br), 4.50(4H,t,*J*=5.7Hz), 4.36(2H,d,*J*=5.4 Hz), 4.00(2H,m), 3.73(1H,m), 3.62(2H,m), 3.40(1H,m)

### Example 30

Compound represented by the structural formula

[0069]

[Com. 41]



20 mg of Compound A and 20 mg of 2-hydroxymethylthiophene-3-carbaldehyde were dissolved in 4 ml of anhydrous methanol, 20 ml of acetic acid was added, and the mixture was stirred at 80°C for 2 hours. The reaction mixture was concentrated under reduced pressure, and the residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness, and the residue was dissolved in 3 ml of a mixed solvent of tetrahydrofuran/methanol (2:1). 30 mg of sodium cyanoborohydride and 300 ml of a 10 % solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure, and the residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 16 mg of the compound represented by the above formula.

R<sub>f</sub> value: 0.49 (Kieselgel 60F<sub>254</sub> made by Merck Co., developing solvent: acetonitrile: tetrahydrofuran: toluene: water: acetic acid = 4:2:2:0.5:0.1)

FAB-MS(m/z):660(M)<sup>+</sup>

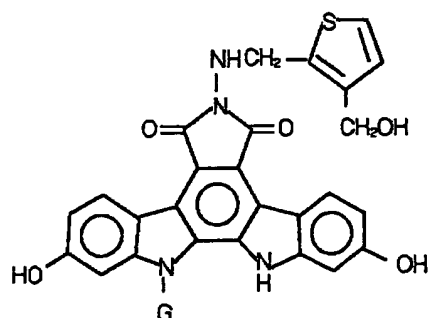
<sup>1</sup>H-NMR(300MHz,DMSO-d<sub>6</sub>,δppm):11.18(1H,s),9.79(1H,s),9.75(1H,s),8.86(1H,d,J=8.4Hz),8.78(1H,d,J=8.4Hz),7.30(1H,d,J=4.8Hz),7.17(1H,d,J=2.1Hz),7.09(1H,d,J=5.4Hz),6.98(1H,d,J=2.1Hz),6.82(1H,dd,J=2.1,8.4Hz),6.80(1H,dd,J=2.1,8.4Hz),5.97(1H,d,J=8.1Hz),5.92(1H,t,J=5.1Hz),5.86(1H,t,J=3.9Hz),5.37(1H,d,J=5.7Hz),5.33(1H,d,J=4.5Hz),5.12(1H,d,J=4.8Hz),4.93(1H,d,J=4.8Hz),4.76(2H,d,J=5.7Hz),4.20(2H,d,J=5.1Hz),4.00(1H,m),3.91(2H,s),3.77(1H,m),3.50(2H,m)

## Example 31

Compound represented by the structural formula

[0070]

[Com. 42]



30 mg of Compound A and 30 mg of 3-t-butyldimethylsilyloxymethylthiophene-2-carbaldehyde were dissolved in 5 ml of anhydrous methanol, 30 ml of acetic acid was added, and the mixture was stirred 80°C for 2 hours. The reaction mixture was concentrated under reduced pressure, and the residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness, and the residue was suspended in 3 ml of methanol. 30 mg of sodium cyanoborohydride and 300 ml of a 10 % solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 1 hours. The reaction mixture was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 24 mg of the compound represented by the above formula.

Rf value: 0.40 (Kieselgel 60F<sub>254</sub> made by Merck Co., developing solvent: acetonitrile: tetrahydrofuran: toluene: water: acetic acid = 4:2:2:0.5:0.1)

FAB-MS(m/z):660(M)<sup>+</sup>

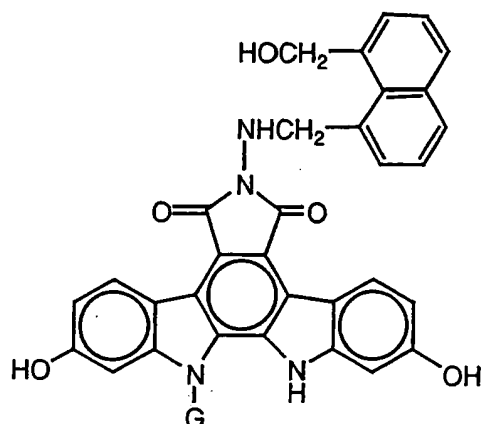
<sup>1</sup>H-NMR(300MHz,DMSO-d<sub>6</sub>,δp pm):11.19(1H,s),9.78(1H,s),9.75(1H,s),8.85(1H,d,J=8.7Hz),8.78(1H,d,J=9.0Hz),7.31(1H,d,J=4.8Hz),7.18(1H,d,J=1.8Hz),6.99(1H,d,J=4.8Hz),6.97(1H,d,J=1.8Hz),6.81(2H,dd,J=1.8,9.0Hz),6.06(1H,t,J=4.8Hz),5.97(1H,d,J=8.7Hz),5.86(1H,t,J=3.9Hz),5.33(1H,d,J=4.5Hz),5.12(1H,d,J=4.5Hz),4.99(1H,t,J=5.4Hz),4.93(1H,d,J=5.1Hz),4.53(2H,d,J=5.7Hz),4.38(2H,d,J=4.8Hz),4.02(1H,m),3.91(2H,m),3.77(1H,m),3.50(2H,m)

#### Example 32

Compound represented by the structural formula

【0071】

【Com. 43】



35 mg of Compound A and 60 mg of 8-t-butyldimethylsilyloxymethyl-1-naphthoaldehyde were suspended in 2 ml of methanol, several drops of acetic acid was added, and the mixture was stirred at 60°C for 2 hours. The reaction mixture was concentrated, and the resulting solid was washed with chloroform to obtain 32.5 mg of an intermediate compound. 68 mg of sodium cyanoborohydride was suspended in 3 ml of tetrahydrofuran, and 0.5 ml of zinc chloride (1.0 M diethyl ether solution) was added dropwise. A suspension of 32.5 mg of the intermediate compound in 2 ml of tetrahydrofuran was added thereto, and the mixture was stirred at room temperature for 2 hours, saturated saline was added, and the mixture was extracted with a mixed solvent of ethyl acetate/methyl ethyl ketone. The organic layer was dried and concentrated, the residue was dissolved in 1.5 ml of tetrahydrofuran, and 0.5 ml of tetrabutylammonium fluoride was added. The mixture was stirred at room temperature for 1.5 hours, diluted with a mixed solvent of ethyl acetate/methyl ethyl ketone, and washed successively with water and saturated saline. The organic layer was dried and concentrated, and the concentrate was placed on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 3.3 mg of the compound represented by the above formula.

FAB-MS (m/z): 705 (M+H)<sup>+</sup>

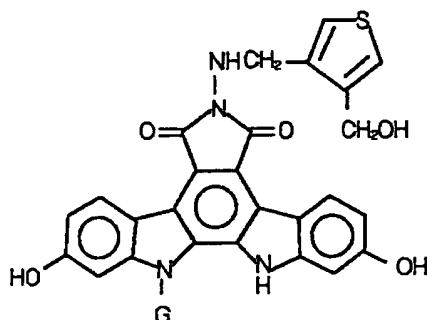
<sup>1</sup>H-NMR (300MHz, DMSO-d<sub>6</sub>, δ ppm) 11.16(1H, s), 8.84(1H, d, J=7.9Hz), 8.76(1H, d, J=7.9Hz), 7.87(2H, d, J=7.4Hz), 7.68(1H, d, J=7.4Hz), 7.58(1H, d, J=7.4Hz), 7.49(1H, d, J=7.4Hz), 7.39(1H, t, J=7.4Hz), 7.15(1H, s), 6.97(1H, s), 6.80(2H, t, J=7.9Hz), 5.86-6.00 (3H, m), 5.42(2H, s), 4.85(2H, d, J=4.2Hz), 4.80-5.50(4H, br), 3.72-4.05(4H, m), 3.45-3.59(2H, m)

### Example 33

Compound represented by the structural formula

[0072]

[Com. 44]



30 mg of Compound A and 30 mg of 4-t-butyltrimethylsilyloxythiophene-3-carbaldehyde were suspended in 6 ml of methanol, 30 ml of acetic acid was added, and the mixture was stirred at 80°C for 2 hours. The reaction mixture was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness, and the residue was dissolved in 5 ml of a mixed solvent of tetrahydrofuran/methanol (2:1). 20 mg of sodium cyanoborohydride and 200 ml of a 10 % solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was diluted with ethyl acetate, washed with water and an aqueous saturated sodium chloride solution, dried and concentrated. The residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 15 mg of the compound represented by the above formula.

Rf value: 0.47 (Kieselgel 60F<sub>254</sub> made by Merck Co., developing solvent: acetonitrile: tetrahydrofuran: toluene: water: acetic acid = 4:2:2:0.5:0.1)

FAB-MS(m/z):661(M+H)<sup>+</sup>

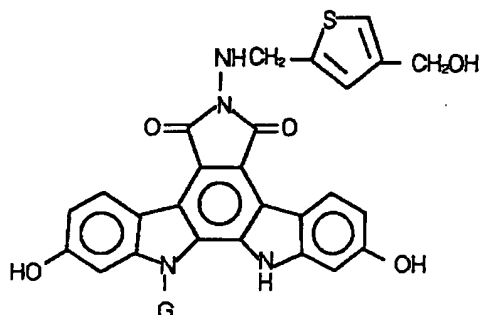
<sup>1</sup>H-NMR(300MHz,DMSO-d<sub>6</sub>,δ ppm):11.19(1H,s),9.79(1H,s),9.76(1H,s),8.86(1H,d,J=8.7Hz),8.78(1H,d,J=8.7Hz),7.43(1H,d,J=3.3Hz),7.30(1H,d,J=3.6Hz),7.17(1H,d,J=2.1Hz),6.98(1H,d,J=2.1Hz),6.83(1H,dd,J=2.1,8.7Hz),6.81(1H,dd,J=2.1,8.7Hz),6.04(1H,t,J=5.1Hz),5.97(1H,d,J=9.0Hz),5.87(1H,t,J=3.6Hz),5.34(1H,d,J=3.9Hz),5.12(1H,d,J=5.1Hz),5.10(1H,t,J=5.1Hz),4.92(1H,d,J=4.5Hz),4.67(2H,d,J=5.4Hz),4.23(2H,d,J=4.2Hz),4.01(1H,m),3.92(2H,s),3.77(1H,m),3.50(2H,m)

Example 34

Compound represented by the structural formula

[0073]

[Com. 45]



38 mg of Compound A and 25 mg of 4-hydroxymethylthiophene-2-carbaldehyde were suspended in 7 ml of anhydrous methanol, 45 ml of acetic acid was added, and the mixture was stirred at 80°C for 7 hours. The reaction mixture was concentrated under reduced pressure, and 38 mg of crystals obtained by filtration from methanol/chloroform. The crystals were dissolved in 10 ml of tetrahydrofuran/methanol (4:1), 13 mg of sodium cyanoborohydride and 0.5 ml of a 10 % solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was diluted with ethyl acetate, washed with an aqueous saturated sodium chloride solution, dried and concentrated. The residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 21.7 mg of the compound represented by the above formula.

Rf value: 0.24 (Kieselgel 60F<sub>254</sub> made by Merck Co., developing solvent: acetonitrile: tetrahydrofuran: toluene: water: acetic acid = 4:2:2:0.5:0.1)

FAB-MS(m/z):660(M<sup>+</sup>)

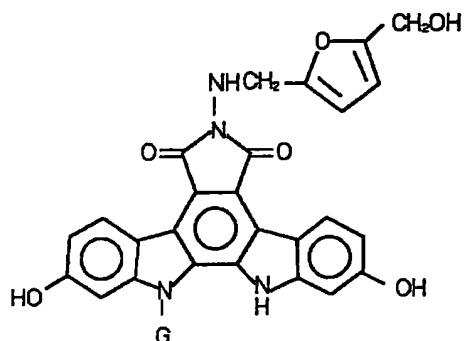
<sup>1</sup>H-NMR(300MHz,DMSO-d<sub>6</sub>,δp pm):11.19(1H,s),9.77(2H,br),8.86(1H,d,J=8.6Hz), 8.78(1H,d,J=8.6Hz),7.17(1H,s),7.14(1H,d,J=1.8Hz),6.98(2H,m),6.81(2H,dt,J=1.8,6.9 Hz),6.12(1H,t,J=5.1Hz),5.97(1H,d,J=8.1Hz),5.87(1H,s),5.35(1H,d,J=1.8Hz),5.13(1H,d ,J=2.4Hz),5.01(1H,t,J=5.4Hz),4.93(1H,d,J=3.6Hz),4.40(2H,d,J=4.5Hz),4.34(2H,d,J=4. 8Hz),4.00(1H,dd,J=2.1,11.6Hz),3.91(2H,s),3.79(1H,m),3.51(2H,br)

#### Example 35

Compound represented by the structural formula

25    [0074]

      [Com. 46]



107 mg of Compound A and 126 mg of 5-hydroxymethylfurfural were suspended in 2 ml of methanol, several drops of acetic acid were added, and the mixture was stirred overnight at 80°C. The reaction mixture was concentrated and the obtained solid was washed with chloroform. The solid was dissolved in 5 ml of a mixed solvent of methanol/tetrahydrofuran (1:2), 62.8 mg of sodium cyanoborohydride and 5 ml of a 10 % solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was diluted with a mixed solvent of ethyl acetate/methyl ethyl ketone, and washed with water and an aqueous saturated sodium chloride solution. The organic layer was dried, concentrated, put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 103 mg of the compound represented by the above formula.

FAB-MS(m/z):644(M)<sup>+</sup>

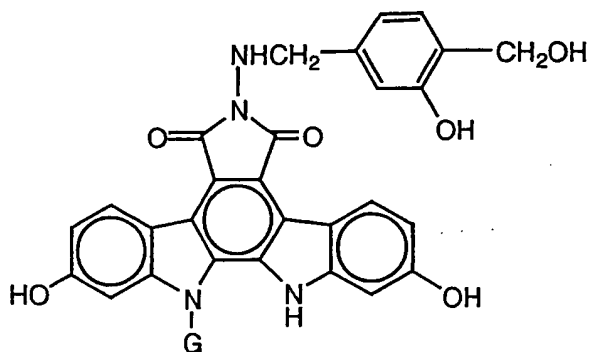
<sup>1</sup>H-NMR(300MHz,DMSO-d<sub>6</sub>,δp pm):11.19(1H,s),9.77(2H,br),8.85(1H,d,J=8.5Hz), 8.77(1H,d,J=8.6Hz),7.18(1H,d,J=2.1Hz),6.98(1H,d,J=1.7Hz),6.75-6.86(2H,m),6.31 (1H,d,J=3.1Hz),6.15(1H,d,J=3.1Hz),6.03(1H,t,J=4.7Hz),5.97(1H,d,J=8.3Hz),5.87(1H,t ,J=3.6Hz),5.34(1H,d,J=3.9Hz),5.08-5.15(2H,m),4.93(1H,d,J=4.5Hz),4.28(2H,d, J=5.6Hz),4.20(2H,d,J=4.7Hz),3.72-4.05(4H,m),3.45-3.55(2H,m)

#### Example 36

Compound represented by the structural formula

[0075]

[Com. 47]



39 mg of Compound A and 33 mg of 3-hydroxy-4-hydroxymethylbenzaldehyde were suspended in 8 ml of methanol, 150μl of acetic acid was added, and the mixture was stirred at room temperature over a period of three nights. The reaction mixture was



filtered, and the resulting solid was washed with chloroform. The solid was dissolved in 5 ml of a mixed solvent of methanol/tetrahydrofuran (1:2), 9 mg of sodium cyanoborohydride and several drops of a 10 % solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated to dryness, and the residue was placed on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 3.5 mg of the compound represented by the above formula.

FAB-MS (m/z): 670 ( $M^+$ )

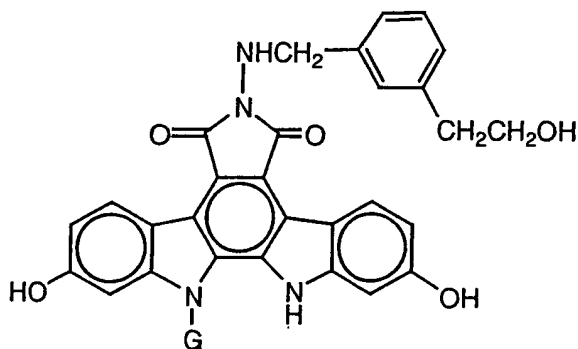
$^1\text{H-NMR}$  (300MHz, DMSO- $d_6$ ,  $\delta$  ppm) 11.18(1H,s), 9.77(1H,s), 9.76(1H,s), 9.28(1H,br), 8.87(1H,d,J=8.5Hz), 8.78(1H,d,J=8.5Hz), 7.18(1H,d,J=7.9Hz), 7.17(1H,s), 6.97(1H,d,J=2.0Hz), 6.77-6.93(4H,m), 5.96(1H,d,J=8.2Hz), 5.92(1H,t,J=5.0Hz), 5.86(1H,t,J=3.2Hz), 5.33(1H,d,J=4.3Hz), 5.12(1H,d,J=4.6Hz), 4.92(1H,d,J=5.0Hz), 5.83(1H,br), 4.41(2H,d,J=3.2Hz), 4.14(2H,d,J=5.0Hz), 4.00(1H,m), 3.90(2H,m), 3.78(1H,m), 3.50(2H,m)

#### Example 37

Compound represented by the structural formula

[0076]

[Com. 48]



30 mg of Compound A and 24.9 mg of 3-(2-hydroxyethyl)benzaldehyde were suspended in 1 ml of methanol, several drops of acetic acid was added, and the mixture was stirred at 80°C for 1 hour. The reaction mixture was concentrated under reduced pressure, and the residue was washed with chloroform. This was suspended in 2 ml of methanol, 9.0 mg of sodium cyanoborohydride and several drops of a 10 % solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was concentrated to dryness, and the residue was placed on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 20.7 mg of the compound represented by the above formula.

FAB-MS (m/z): 669 ( $M+H^+$ )

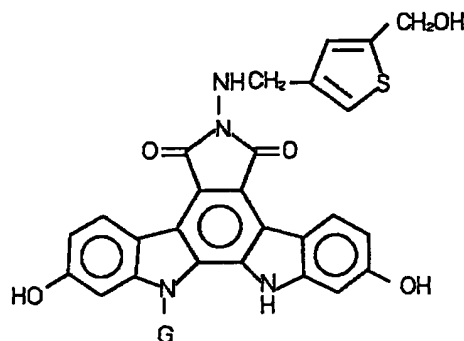
$^1\text{H-NMR}$  (300MHz, DMSO- $d_6$ ,  $\delta$  ppm) 11.18(1H,s), 9.78(1H,s), 9.75(1H,s), 8.87(1H,d,J=8.5Hz), 8.79(1H,d,J=8.6Hz), 7.36(1H,s), 7.32(1H,d,J=7.6Hz), 7.15-7.25 (2H,m), 7.07(1H,d,J=7.6Hz), 6.97(1H,d,J=2.0Hz), 6.75-6.85(2H,m), 6.02(1H,d,J=5.2Hz), 5.96(1H,d,J=8.2Hz), 5.86(1H,t,J=3.3Hz), 5.33(1H,d,J=4.3Hz), 5.11(1H,d,J=4.9Hz), 4.90(1H,d,J=5.4Hz), 4.61(1H,t,J=5.3Hz), 4.23(2H,d,J=4.5Hz), 3.72-4.05(4H,m), 3.45-3.60(4H,m), 2.69(2H,t,J=7.3Hz)

## Example 38

Compound represented by the structural formula

[0077]

[Com. 49]



40 mg of Compound A and 40 mg of 5-hydroxymethylthiophene-3-carbaldehyde were suspended in 8 ml of methanol, 40 ml of acetic acid was added, and the mixture was stirred at 80°C for 3 hours. The reaction mixture was cooled to room temperature, chloroform was added, and the resulting powder was obtained by filtration. This was suspended in 5 ml of methanol, 20 mg of sodium cyanoborohydride and 200 ml of a 10 % solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was diluted with a mixed solvent of ethyl acetate/methyl ethyl ketone, washed with water and an aqueous saturated sodium chloride solution, dried, and concentrated. The residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 21 mg of the compound represented by the above formula.

R<sub>f</sub> value: 0.29 (Kieselgel 60F<sub>254</sub> made by Merck Co., developing solvent: acetonitrile: tetrahydrofuran: toluene: water: acetic acid = 4:2:2:0.5:0.1)

FAB-MS(m/z):660(M<sup>+</sup>)

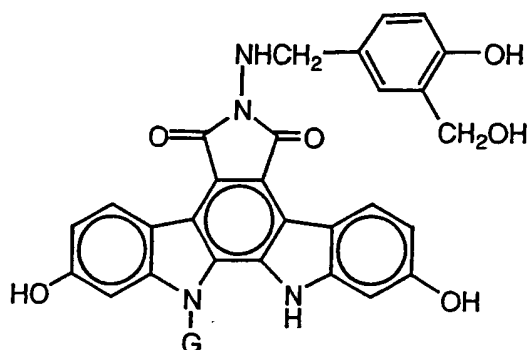
<sup>1</sup>H-NMR(300MHz,DMSO-d<sub>6</sub>,δppm):11.19(1H,s),9.80(2H,br),8.86(1H,d,J=9.0Hz), 8.79(1H,d,J=8.7Hz),7.34(1H,s),7.17(1H,d,J=1.5Hz),7.04(1H,s),6.97(1H,d,J=1.5Hz),6.82(1H,dd,J=1.5,9.0Hz),6.80(1H,dd,J=8.7,1.5Hz),5.97(2H,t,J=5.1Hz),5.87(1H,br),5.40(1H,t,J=6.0Hz),5.35(1H,br),5.13(1H,s),4.91(1H,d,J=3.9Hz),4.57(2H,d,J=4.2Hz),4.20(2H,d,J=4.8Hz),3.88-4.10(3H,m),3.78(1H,m),3.50(2H,m)

## Example 39

Compound represented by the structural formula

[0078]

[Com. 50]



38 mg of Compound A and 91 mg of 3-hydroxymethyl-4-hydroxybenzaldehyde were dissolved in 2 ml of N,N-dimethylformamide, three drops of acetic acid was added, and the mixture was stirred at 80°C for 3 hour. The reaction mixture was concentrated under reduced pressure, and the residue was washed with chloroform. This was suspended in 3 ml of methanol, 40 mg of sodium cyanoborohydride and several drops of a 10 % solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was placed on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 8.9 mg of the compound represented by the above formula.

Rf value: 0.15 (Kieselgel 60F<sub>254</sub> made by Merck Co., developing solvent ; acetonitrile:tetrahydrofuran:toluene:water:acetic acid=4:2:2:0.5:0.1)

FAB-MS (m/z):

<sup>1</sup>H-NMR (300MHz,DMSO-d<sub>6</sub>,δp pm) 11.19(1H,s),9.75(1H,br),9.74(1H,br),9.23(1H,br),8.87(1H,d,J=8.6Hz),8.79(1H,d,J=8.6Hz),7.37(1H,s),7.12-7.20(2H,m),6.98(1H,d,J=2.1Hz),6.75-6.85(2H,m),6.70(1H,d,J=8.3Hz),5.97(1H,d,J=8.3Hz),5.86(1H,t,J=4.4Hz),5.76(1H,t,J=5.3Hz),5.33(1H,d,J=4.4Hz),5.10(1H,d,J=3.4Hz),4.89-4.98(2H,m),4.44(2H,d,J=4.5Hz),3.72-4.15(6H,m),3.48-3.55(2H,m)

【0079】

【Effect of the Invention】

The compounds of the invention have excellent antitumor effect, and are useful as antitumor agents in the field of medicine.

【0080】

Continued from the front page

(72) Inventor

Mitsuru OHKUBO  
c/o Banyu Pharmaceutical Co., Ltd.  
Tsukuba Research Institute  
3, Okubo, Tsukuba-shi, Ibaraki

(72) Inventor

Hiroyuki SUDA  
c/o Banyu Pharmaceutical Co., Ltd.  
Tsukuba Research Institute  
3, Okubo, Tsukuba-shi, Ibaraki

(51) Int.Cl.<sup>6</sup>

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(71) 出願人 000005072

萬有製薬株式会社

東京都中央区日本橋本町2丁目2番3号

(72) 発明者 小尻 勝久

茨城県つくば市大久保3番地 萬有製薬株式会社つくば研究所内

(72) 発明者 近藤 久雄

茨城県つくば市大久保3番地 萬有製薬株式会社つくば研究所内

(72) 発明者 荒川 浩治

茨城県つくば市大久保3番地 萬有製薬株式会社つくば研究所内

最終頁に続く

(54) 【発明の名称】 抗腫瘍性インドロピロカルバゾール誘導体

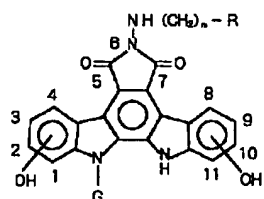
(57) 【要約】

【課題】 新規抗腫瘍剤の創製。

【解決手段】 一般式

【化1】

ドロキシ基の置換位置は1位と11位又は2位と10位である】で表される化合物又はその医薬上許容される塩。



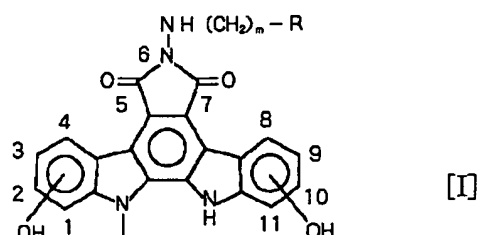
[1]

〔式中、Rはヒドロキシ基、低級アルコキシ基、ヒドロキシ低級アルキル基及びヒドロキシ低級アルケニル基からなる群から選ばれる1又は2個の置換基を有するフェニル基、ナフチル基、ピリジル基、フリル基又はチエニル基（但し、置換基として低級アルコキシ基を有する場合は、同時にヒドロキシ基、低級アルコキシ基、ヒドロキシ低級アルキル基及びヒドロキシ低級アルケニル基からなる群から選ばれるもう一つの置換基を有する）を示し、mは1～3の整数を示し、Gはβ-D-グルコピラノシル基を示し、インドロピロカルバゾール環上のヒ

【特許請求の範囲】

【請求項 1】 一般式

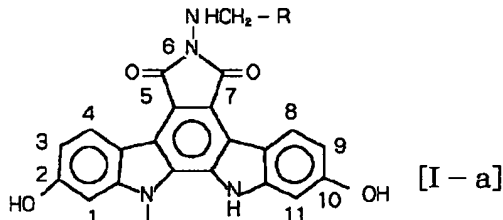
【化 1】



【式中、Rはヒドロキシ基、低級アルコキシ基、ヒドロキシ低級アルキル基及びヒドロキシ低級アルケニル基からなる群から選ばれる1又は2個の置換基を有するフェニル基、ナフチル基、ピリジル基、フリル基又はチエニル基（但し、置換基として低級アルコキシ基を有する場合は、同時にヒドロキシ基、低級アルコキシ基、ヒドロキシ低級アルキル基及びヒドロキシ低級アルケニル基からなる群から選ばれるもう一つの置換基を有する）を示し、mは1～3の整数を示し、Gはβ-D-グルコピラノシル基を示し、インドロピロロカルバゾール環上のヒドロキシ基の置換位置は1位と11位又は2位と10位である】で表される化合物又はその医薬上許容される塩。

【請求項 2】 一般式

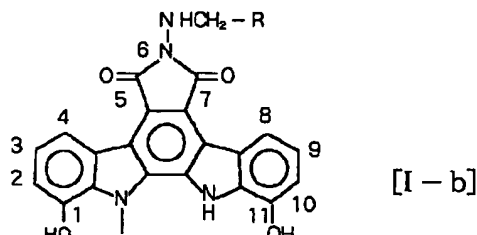
【化 2】



【式中、R、m及びGは請求項 1 記載の意味を有する】で表される請求項 1 記載の化合物又はその医薬上許容される塩。

【請求項 3】 一般式

【化 3】



【式中、R、m及びGは請求項 1 記載の意味を有する】で表される請求項 1 記載の化合物又はその医薬上許容される塩。

【請求項 4】 請求項 1、2 又は 3 に記載の化合物又はその医薬上許容される塩を含有することを特徴とする抗腫瘍剤。

【発明の詳細な説明】

【0001】

【産業上の利用分野】 本発明は医薬の分野で有用であり、さらに詳細には腫瘍細胞の増殖を阻害し、抗腫瘍効果を発揮する新規なインドロピロロカルバゾール誘導体、その製法及びその用途に関する。

【0002】

【従来の技術】 癌化学療法分野においては、すでに多数の化合物が医薬として実用化されている。しかしながら、様々な種類の腫瘍に対してその効果は必ずしも充分ではなく、またこれらの薬剤に対する腫瘍細胞の耐性の問題も臨床上的使用法を複雑にしている【第47回日本癌学会総会記事、12～15頁（1988年）参照】。

【0003】 このような状況下、癌治療の分野においては常に新規制癌物質の開発が求められている。特に、既存の制癌物質に対する耐性を克服し、既存の制癌物質が十分に効果を発揮できない種類の癌に対して有効性を示す物質が必要とされている。

【0004】 このような現状に鑑み、本発明者らは広く微生物代謝産物をスクリーニングした結果、抗腫瘍活性を有する新規な化合物 BE-13793C（12, 13-ジヒドロ-1, 11-ジヒドロキシ-5H-インドロ[2, 3-a]ピロロ[3, 4-c]カルバゾール-5, 7（6H）-ジオン）を見出した（ヨーロッパ特許公開公報 0388956A2 参照）。

【0005】 その後、BE-13793C に化学修飾を加えて更に優れた抗腫瘍活性を有する化合物を創製することを試み、先の特許出願（ヨーロッパ特許公開公報 0528030A1、ヨーロッパ特許公開公報 0545195A1、WO95/30682 及び WO96/04293）において開示した。

【0006】

【発明が解決しようとする課題】 先の特許出願において開示したインドロピロロカルバゾール系の抗腫瘍性物質に化学修飾を施し、更に優れた抗腫瘍活性を有する化合物を創製することが本発明が解決しようとする課題である。

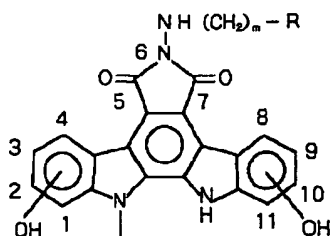
【0007】

【課題を解決するための手段】 本発明者等は、上記課題を解決すべく、インドロピロロカルバゾール誘導体を広く合成し、抗腫瘍活性について検討した結果、後記一般式 [I] で表される化合物が、上記、先の特許出願において開示したインドロピロロカルバゾール化合物よりも更に優れた抗腫瘍作用を示すことを見だして本発明を完成した。

【0008】 即ち、本発明は一般式

【0009】

【化 4】



[I]

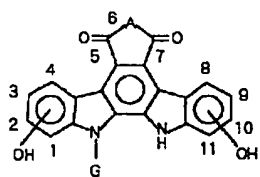
〔式中、Rはヒドロキシ基、低級アルコキシ基、ヒドロキシ低級アルキル基及びヒドロキシ低級アルケニル基からなる群から選ばれる1又は2個の置換基を有するフェニル基、ピリジル基、フリル基又はチエニル基（但し、置換基として低級アルコキシ基を有する場合は、同時にヒドロキシ基、低級アルコキシ基、ヒドロキシ低級アルキル基及びヒドロキシ低級アルケニル基からなる群から選ばれるもう一つの置換基を有する）を示し、mは1～3の整数を示し、Gはβ-D-グルコピラノシル基を示し、インドロピロカルバゾール環上のヒドロキシ基の置換位置は1位と11位又は2位と10位である〕で表される化合物又はその医薬上許容される塩及びその用途に関するものである。

【0010】次に本発明化合物の製造法について説明する。

【0011】本発明のインドロピロカルバゾール誘導体は、ヨーロッパ特許公開公報0528030A1、ヨーロッパ特許公開公報0545195A1、WO95/30682及びWO96/04293に記載の公知化合物である、一般式

【0012】

〔化5〕



[II]

〔式中、AはNH又はHを示し、Gは前記の意味を有する〕で表される化合物に、一般式

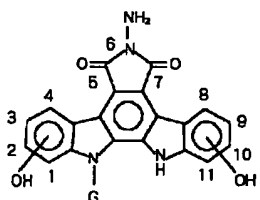
【0013】

〔化6〕

〔式中、R及びmは前記の意味を有する〕で表される化合物を反応させるか、一般式

【0014】

〔化7〕



[IV]

〔式中、Gは前記の意味を有する〕で表される化合物と、一般式

【0015】

〔化8〕

〔式中、R<sup>1</sup>はRと同様の意味を有するがRに有する水酸基が保護された基を意味し、mは前記の意味を有する〕で表される化合物を縮合させ、次いで還元し、そして必要に応じて保護基の除去を行うことにより製造するか、又は一般式〔I V〕の化合物に、一般式

【0016】

〔化9〕

〔式中、Lは脱離基を示し、R<sup>1</sup>及びmは前記と同様の意味を有する〕で表される化合物を反応させ、そして必要に応じて保護基の除去を行うことにより製造することができる。

【0017】一般式〔I I〕で表される化合物と一般式〔I I I〕で表される化合物との反応は化学の分野で広く知られたイミド又は酸無水物とヒドラジン誘導体との反応である。この反応は、通常反応に悪影響を及ぼさない溶媒、例えばテトラヒドロフラン、N、N-ジメチルホルムアミド等を用いて行うことができ、化合物〔I I I〕の使用量は化合物〔I I〕に対して通常少過剰から5モル当量であるが、必要に応じて大過剰用いて行うこともできる。

【0018】反応温度は通常-50℃～溶媒の沸点の範囲であり、必要に応じてこれ以上又はこれ以下の温度を選択することもできる。反応時間は通常30分～2日間の範囲であるが必要に応じてこれ以上又はこれ以下の時間で行うことができる。

【0019】また一般式〔I V〕で表される化合物と一般式〔V〕で表される化合物を縮合させ、ついで還元して化合物〔I〕を製造する反応は、同一の反応系で行うことができるが、場合により中間生成物であるシッフ塩基を一旦単離することもできる。すなわち通常、化合物〔I V〕と化合物〔V〕を適当な溶媒中で混合し、次いで還元剤を添加することにより行うことができる。この際、酢酸、塩酸等の酸の存在下に反応を行うことが好ましい。ここで使用できる溶媒としては、例えばメタノール、エタノール等のアルコール系溶媒、N、N-ジメチルホルムアミド等の非プロトン性極性溶媒等を挙げることができる。シッフ塩基の還元は、シアノ水素化ほう素ナトリウム等の水素化金属錯体等を用いて行うことができるが、また接触還元法により行うこともできる。

【0020】また一般式〔I V〕の化合物と一般式〔V I〕の反応は、アミンのアルキル化反応であり、公知の方法、例えばアルキルハライド、アルキルメシレート又はアルキルトシレート等との反応等により行うことができる。

【0021】また、上記反応の生成物は有機合成化学の分野における公知の方法、例えば沈澱法、溶媒抽出法、再結晶、クロマトグラフィー法等により精製することができる。

【0022】更に本発明には、上記方法で得られる化合物の医薬上許容される塩も包含される。このような塩としては例えばカリウム、ナトリウム等のアルカリ金属との塩、例えばカルシウム等のアルカリ土類金属との塩、又は例えばエチルアミン及びアルギニン等の塩基性有機化合物との塩、例えば塩酸、硫酸等の無機酸との塩又は例えば酢酸、クエン酸、マレイン酸等の有機酸との塩を挙げることができる。

【0023】本発明の式【I】で表される化合物は、優れた抗腫瘍作用を示す。

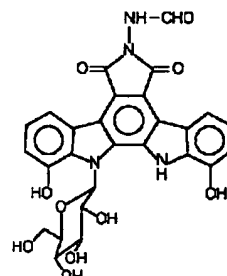
#### 【0024】ヒト胃癌MX-1に対する効果

予めヌードマウス皮下に移植し、増殖させたMX-1固型腫瘍を細切し、その3mm角を被験マウス皮下に移植した。移植後、腫瘍が0.3cm<sup>3</sup>に増殖した時点より各量の試験薬物をマウス尾静脈に1日1回5日間連続注射し、2日休薬後更に5日間注射（治療スケジュール：

5/w×2）又は3～4日毎に4回（治療スケジュール：2/w×2）注射し治療した。治療開始20日後又は32日後に腫瘍の長径（L）及び短径（W）を測定し、その体積（V）を求めた（ $V = 1/2 \times L \times W^2$ ）。この体積より腫瘍増殖阻害率を算出し、腫瘍増殖を75%抑制する投与総量（GID<sub>75</sub>, mg/kg）を求めた。対照化合物としては、式

【0025】

【化10】



の化合物を用いた。結果を第1表に示した。

【0026】

【表1】

第1表 本発明化合物のヒト胃癌MX-1に対する効果		
供試化合物	治療スケジュール	GID <sub>75</sub> (mg/kg total)
実施例3	2/w×2	< 90
実施例5	5/w×2	< 90
実施例10	5/w×2	< 90
実施例12	2/w×2	97
実施例14	2/w×2	< 12
実施例27	2/w×2	< 4.5
実施例28	2/w×2	< 36
実施例30	5/w×2	16
実施例31	5/w×2	< 30
実施例33	5/w×2	< 30
実施例35	5/w×2	82
実施例36	5/w×2	< 30
実施例37	5/w×2	32
実施例38	5/w×2	19
実施例39	2/w×2	< 30
対照化合物	5/w×2	1900

本発明により提供される化合物は、対照化合物に比べ、上記の薬理試験結果に示される如く更に優れた抗腫瘍作用を示す。

【0027】上記の薬理試験の結果から明らかなように、本発明の化合物は優れた抗腫瘍作用を示し、抗腫瘍剤として疾病の予防・治療のため、殊に癌の処置のために有用である。本発明化合物を抗腫瘍剤として使用する際の投与形態としては各種の形態を選択でき、例えば錠剤、カプセル剤、散剤、顆粒剤若しくは液剤等の経口剤、又は例えば溶液若しくは懸濁液等の殺菌した液状の非経口剤が挙げられる。

【0028】固体の製剤は、そのまま錠剤、カプセル

剤、顆粒剤又は粉末の形態として製造することもできるが、適当な添加物を使用して製造することもできる。そのような添加物としては、例えば乳糖若しくはブドウ糖等の糖類、例えばトウモロコシ、小麦若しくは米等の澱粉類、例えばステアリン酸等の脂肪酸、例えばメタケイ酸アルミン酸マグネシウム若しくは無水リン酸カルシウム等の無機塩、例えばポリビニルピロリドン若しくはポリアルキレングリコール等の合成高分子、例えばステアリン酸カルシウム若しくはステアリン酸マグネシウム等の脂肪酸塩、例えばステアリルアルコール若しくはベンジルアルコール等のアルコール類、例えばメチルセルロース、カルボキシメチルセルロース、エチルセルロース

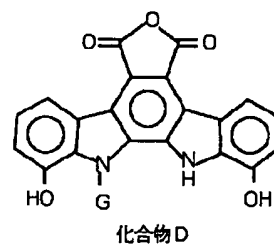
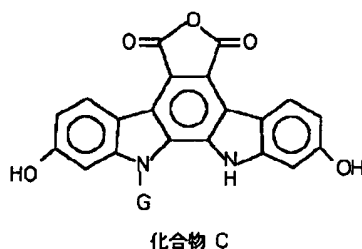
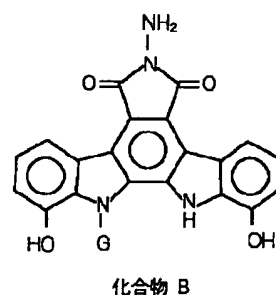
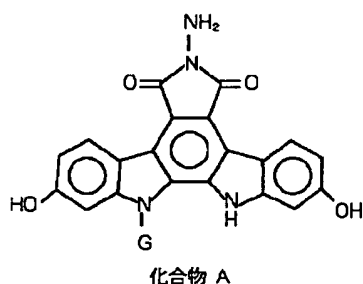
若しくはヒドロキシプロピルメチルセルロース等の合成セルロース誘導体、その他、水、ゼラチン、タルク、植物油、アラビアゴム等通常用いられる添加物が挙げられる。

【0029】これらの錠剤、カプセル剤、顆粒剤及び粉末等の固形製剤は一般的には0.1～100重量%、好ましくは5～100重量%の有効成分を含む。

【0030】液状製剤は、水、アルコール類又は例えば大豆油、ピーナツ油若しくはゴマ油等の植物由来の油等液状製剤において通常用いられる適当な添加物を使用し、懸濁液、シロップ剤若しくは注射剤等の形態として製造される。

【0031】特に、非経口的に筋肉内注射、静脈内注射又は皮下注射で投与する場合の適当な溶剤としては、例えば注射用蒸留水、塩酸リドカイン水溶液（筋肉内注射用）、生理食塩水、ブドウ糖水溶液、エタノール、ポリエチレングリコール、静脈内注射用液体（例えばクエン酸及びクエン酸ナトリウム等の水溶液）若しくは電解質溶液（点滴静注及び静脈内注射用）等、又はこれらの混合溶液が挙げられる。

【0032】これらの注射剤は予め溶解したもの他、粉末のまま或いは適当な添加物を加えたものを用時溶解する形態もとて得る。これらの注射液は、通常0.1～10重量%、好ましくは1～5重量%の有効成分を含む。



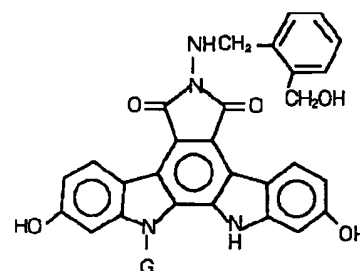
式中、Gはβ-D-グルコピラノシル基を示す。以下の実施例において同じ。

実施例 1

構造式

【0039】

【化12】



で表される化合物。

む。

【0033】また、経口投与の懸濁剤又はシロップ剤等の液剤は、0.5～10重量%の有効成分を含む。

【0034】本発明の化合物の実際に好ましい投与量は、使用される化合物の種類、配合された組成物の種類、適用頻度及び治療すべき特定部位、宿主及び腫瘍によって変化することに注意すべきである。例えば、1日当りの成人1人当りの投与量は、経口投与の場合、10ないし500mgであり、非経口投与、好ましくは静脈内注射の場合、1日当り10ないし100mgである。なお、投与回数は投与方法及び症状により異なるが、1回ないし5回である。また、隔日投与、隔々日投与などの間歇投与等の投与方法も用いることができる。

【0035】

【発明の実施の形態】

【0036】

【実施例】以下に実施例を挙げて本発明をより具体的に説明するが、本発明はこれら実施例のみに限定されるものではない。

【0037】なお、実施例において原料として用いた以下の構造式を有する化合物を下記のとおり略称する。

【0038】

【化11】



【0040】化合物A 25mgと(2-*t*-ブチルジメチルシリルオキシメチル)ベンジルブロミド90mgをN,N-ジメチルホルムアミド1mlに溶解し、室温で一晩攪拌した。反応液を減圧乾固した残渣をセファデックスLH-20のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮し、再びセファデックスLH-20のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固し、残渣をクロロホルムで洗浄することにより、表題の式で表される化合物3.6mgを得た。

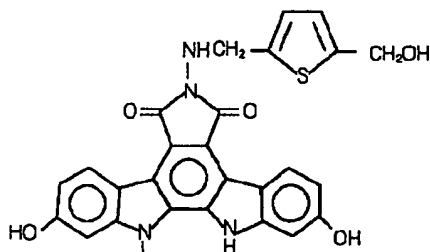
FAB-MS ( $m/z$ ) : 655 ( $M+H$ )<sup>+</sup>  
<sup>1</sup>H-NMR (300MHz, DMSO-*d*<sub>6</sub>,  $\delta$  ppm) : 11.19 (1H, s), 9.78 (1H, s), 9.75 (1H, s), 8.86 (1H, d,  $J=8.6$ Hz), 8.78 (1H, d,  $J=8.2$ Hz), 7.44 (1H, d,  $J=7.2$ Hz), 7.37 (1H, d,  $J=7.6$ Hz), 7.13-7.28 (3H, m), 6.98 (1H, s), 6.78-6.88 (2H, m), 5.95-6.05 (2H, m), 5.85 (1H, br), 5.33 (1H, d,  $J=3.2$ Hz), 5.10-5.17 (2H, m), 4.92 (1H, d,  $J=4.0$ Hz), 4.28 (2H, d,  $J=5.2$ Hz), 3.72-4.10 (4H, m), 3.45-3.55 (2H, m)

#### 実施例2

##### 構造式

【0041】

【化13】



で表される化合物。化合物A 30mgと(5-*t*-ブチルジメチルシリルオキシメチルチオフェン)-2-カルボキシアレヒド30mgをメタノール6mlに溶解し、酢酸30mlを加え、80℃で4時間攪拌した。反応液を室温に冷却し、シアノ水素化ほう素ナトリウム20mg、10%塩酸メタノール溶液200mlを加え、室温で30分間攪拌した。反応液を減圧乾固した残渣をセファデックスLH-20のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物27mgを得た。

Rf値: 0.37 (メルク社製、キーゼーゲル60F<sub>254</sub>, 展開溶媒; アセトニトリル: テトラヒドロフラン: トルエン: 水: 酢酸=4:2:2:0.5:0.1)

FAB-MS ( $m/z$ ) : 660 ( $M^+$ )

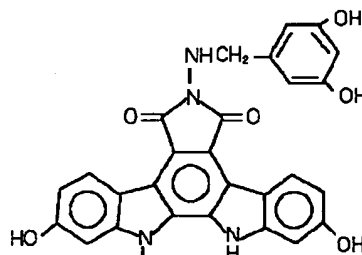
<sup>1</sup>H-NMR (300MHz, DMSO-*d*<sub>6</sub>,  $\delta$  ppm) : 11.19 (1H, s), 9.79 (1H, s), 9.75 (1H, s), 8.86 (1H, d,  $J=9.3$ Hz), 8.78 (1H, d,  $J=9.0$ Hz), 7.17 (1H, d,  $J=2.1$ Hz), 6.97 (1H, d,  $J=2.1$ Hz), 6.89 (1H, d,  $J=3.6$ Hz), 6.82 (1H, dd,  $J=2.1, 9.3$ Hz), 6.79 (1H, dd,  $J=2.1, 9.0$ Hz), 6.73 (1H, d,  $J=3.3$ Hz), 6.10 (1H, t,  $J=4.5$ Hz), 5.97 (1H, d,  $J=8.1$ Hz), 5.86 (1H, t,  $J=3.3$ Hz), 5.35 (1H, t,  $J=6.0$ Hz), 5.32 (1H, d,  $J=4.8$ Hz), 5.12 (1H, d,  $J=4.8$ Hz), 4.92 (1H, d,  $J=5.4$ Hz), 4.52 (2H, d,  $J=5.7$ Hz), 4.40 (2H, d,  $J=4.2$ Hz), 4.02 (1H, m), 3.91 (2H, m), 3.78 (1H, m), 3.50 (2H, m)

#### 実施例3

##### 構造式

【0042】

【化14】



で表される化合物。化合物A 100mgと3,5-ジヒドロキシベンズアルデヒド131.2mgをN,N-ジメチルホルムアミド10mlに溶解し、80℃で48時間攪拌した。反応液を減圧濃縮後、残渣をセファデックスLH-20のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固し、90.3mgの中間化合物を得た。この中間化合物20mgをメタノール5mlに懸濁し、シアノ水素化ほう素ナトリウム10mg、10%塩酸メタノール溶液数滴を加え、室温で30分間攪拌した。メタノールを減圧留去後、水を加え、酢酸エチルで抽出した。有機層を飽和食塩水で洗浄、乾燥濃縮した残渣をセファデックスLH-20のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物18mgを得た。

Rf値: 0.30 (メルク社製、キーゼーゲル60F<sub>254</sub>, 展開溶媒; アセトニトリル: テトラヒドロフラン: トルエン: 水: 酢酸=4:2:2:0.5:0.1)

FAB-MS ( $m/z$ ) : 657 ( $M+H^+$ )

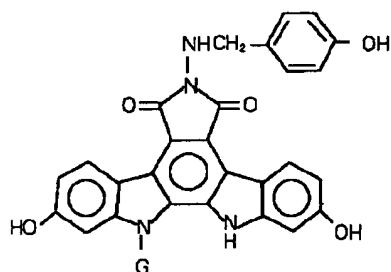
$^1H$ -NMR (300MHz, DMSO- $d_6$ ,  $\delta$  ppm) : 11.19 (1H, s), 9.77 (2H, br), 9.11 (2H, s), 8.87 (1H, d,  $J=8.6$ Hz), 8.79 (1H, d,  $J=8.6$ Hz), 7.17 (1H, s), 6.97 (1H, s), 6.78~6.84 (2H, m), 6.34 (2H, s), 6.06 (1H, s), 5.96 (1H, d,  $J=8.3$ Hz), 5.83~5.87 (2H, m), 5.34 (1H, s), 5.12 (1H, s), 4.92 (1H, d,  $J=3.9$ Hz), 4.04 (2H, d,  $J=4.5$ Hz), 3.91~3.99 (3H, m), 3.75~3.88 (1H, m), 3.49 (2H, s)

#### 実施例4

##### 構造式

【0043】

【化15】



で表される化合物。化合物A 30mgと4-ヒドロキシベンズアルデヒド 14mgをメタノール6mlに溶解し、酢酸 14mlを加え、80℃で2時間攪拌した。反応液を室温に冷却し、シアノ水素化ほう素ナトリウム 20mg、10%塩酸メタノール溶液 200mlを加え、室温で1時間攪拌した。反応液をセファデックス LH-20のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物 31mgを得た。

Rf値: 0.41 (メルク社製、キーゼルゲル 60F<sub>254</sub>, 展開溶媒; アセトニトリル: テトラヒドロフラン: トルエン: 水: 酢酸 = 4: 2: 2: 0.5: 0.1)

FAB-MS ( $m/z$ ) : 640 ( $M^+$ )

$^1H$ -NMR (300MHz, DMSO- $d_6$ ,  $\delta$  ppm) : 11.17 (1H, s), 9.77 (1H, s), 9.74 (1H, s), 9.24 (1H, s), 8.86 (1H, d,  $J=8.4$ Hz), 8.78 (1H, d,  $J=8.4$ Hz), 7.25 (2H, d,  $J=8.7$ Hz), 7.17 (1H, d,  $J=1.8$ Hz), 6.97 (1H, d,  $J=1.8$ Hz), 6.83 (1H, dd,  $J=1.8, 8.7$ Hz), 6.80 (1H, dd,  $J=1.8, 8.7$ Hz), 6.67 (2H, d,  $J=8.1$ Hz), 5.96 (1H, d,

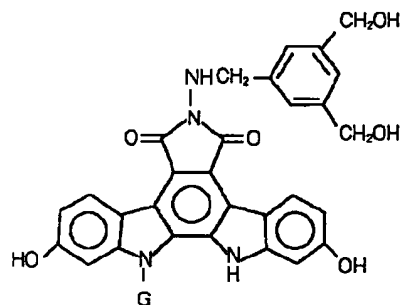
$J=8.1$ Hz), 5.87 (1H, t,  $J=4.8$ Hz), 5.85 (1H, t,  $J=3.9$ Hz), 5.32 (1H, d,  $J=4.5$ Hz), 5.10 (1H, d,  $J=5.1$ Hz), 4.91 (1H, d,  $J=4.8$ Hz), 4.12 (2H, m), 4.03 (1H, m), 3.91 (2H, s), 3.78 (1H, m), 3.50 (2H, m)

#### 実施例5

##### 構造式

【0044】

【化16】



で表される化合物。化合物A 30mgと3,5-ジヒドロキシメチルベンズアルデヒド 20mgをメタノール6mlに溶解し、酢酸 20mlを加え、80℃で3時間攪拌した。反応液を室温に戻し、シアノ水素化ほう素ナトリウム 10mg、10%塩酸メタノール溶液数滴を加え、室温で30分間攪拌した。反応液をセファデックス LH-20のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物 22mgを得た。

Rf値: 0.35 (メルク社製、キーゼルゲル 60F<sub>254</sub>, 展開溶媒; アセトニトリル: テトラヒドロフラン: トルエン: 水: 酢酸 = 4: 2: 2: 0.5: 0.1)

FAB-MS ( $m/z$ ) : 684 ( $M^+$ )

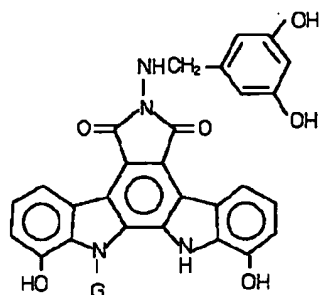
$^1H$ -NMR (300MHz, DMSO- $d_6$ ,  $\delta$  ppm) : 11.19 (1H, s), 9.79 (1H, s), 9.76 (1H, s), 8.88 (1H, d,  $J=8.7$ Hz), 8.80 (1H, d,  $J=8.7$ Hz), 7.32 (2H, s), 7.18 (2H, s), 6.98 (1H, d,  $J=1.8$ Hz), 6.81 (2H, dt,  $J=1.8, 8.7$ Hz), 5.97 (1H, d,  $J=8.7$ Hz), 5.93 (1H, t,  $J=4.8$ Hz), 5.87 (1H, t,  $J=3.2$ Hz), 5.34 (1H, d,  $J=4.2$ Hz), 5.15 (2H, t,  $J=6.3$ Hz), 5.12 (1H, d,  $J=4.8$ Hz), 4.92 (1H, d,  $J=4.8$ Hz), 4.49 (2H, s), 4.47 (2H, s), 4.22 (2H, d,  $J=5.1$ Hz), 4.03 (1H, m), 3.92 (2H, s), 3.78 (1H, m), 3.50 (2H, m)

実施例6

構造式

【0045】

【化17】



で表される化合物。化合物B 53 mgと3, 5-ジヒドロキシベンズアルデヒド 69 mgをN, N-ジメチルホルムアミド 3 mlに溶解し、80℃で一晩撹拌した。反応液を減圧濃縮後、メタノール 10 mlに溶解し、過剰量のシアノ水素化ほう素ナトリウム、10%塩酸メタノール溶液 0.5 mlを加え、室温で30分間撹拌した。反応液を減圧濃縮後、水を加え、酢酸エチル/メチルエチルケトン混合溶媒で抽出し、有機層を、飽和食塩水で洗浄後、乾燥濃縮した。残渣をセファデックス LH-20のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物 4.8 mgを得た。

Rf値: 0.2 (メルク社製, キーゼルゲル 60 F<sub>254</sub>, 展開溶媒; クロロホルム: メタノール=3:1)

FAB-MS (m/z): 657 (M+H)<sup>+</sup>

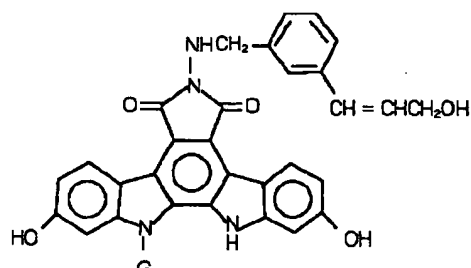
<sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>, δ ppm): 10.89 (1H, s), 10.33 (1H, br), 9.97 (1H, br), 9.11 (1H, s), 8.70 (1H, d, J=6.8 Hz), 8.52 (1H, d, J=7.7 Hz), 7.15~7.21 (2H, m), 6.98~7.06 (3H, m), 6.36 (2H, d, J=1.9 Hz), 6.06 (1H, s), 5.91 (1H, t, J=5.4 Hz), 5.41 (1H, d, J=5.6 Hz), 5.30~5.45 (1H, m), 5.20 (1H, d, J=4.6 Hz), 4.87 (1H, m), 3.94~4.10 (4H, m), 3.56~3.77 (3H, m), 3.38~3.43 (2H, m)

実施例7

構造式

【0046】

【化18】



で表される化合物。化合物C 30 mgと3-(3-ヒドロキシプロペニル)ベンジルヒドラジン トリフルオロ酢酸塩 30 mgをN, N-ジメチルホルムアミド 2 mlに溶解し、トリエチルアミン数滴を加え、80℃で一晩撹拌した。反応液を濃縮乾固後、残渣を分取薄層クロマトグラフィー (展開溶媒; アセトニトリル: テトラヒドロフラン: トルエン: 水: 酢酸=4:2:2:0.5:0.1) により、精製した。表題の式で表される化合物 8.2 mgを得た。

Rf値: 0.51 (メルク社製, キーゼルゲル 60 F<sub>254</sub>, 展開溶媒; アセトニトリル: テトラヒドロフラン: トルエン: 水: 酢酸=4:2:2:0.5:0.1)

FAB-MS (m/z):

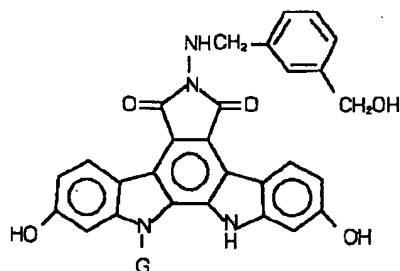
<sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>, δ ppm): 11.18 (1H, s), 9.50~10.00 (2H, br), 8.86 (1H, d, J=8.1 Hz), 8.78 (1H, d, J=8.5 Hz), 7.59 (1H, s), 7.20~7.40 (3H, m), 7.16 (1H, s), 6.97 (1H, s), 6.73~6.89 (2H, m), 6.42 (1H, d, J=3.6 Hz), 6.31~6.48 (1H, m), 6.10 (1H, t, J=4.0 Hz), 5.95 (1H, d, J=7.9 Hz), 5.88 (1H, br), 5.36 (1H, br), 5.13 (1H, br), 4.91 (1H, br), 4.84 (1H, br), 4.26 (2H, s), 4.09 (2H, s), 3.70~4.10 (4H, m), 3.41~3.58 (2H, m)

実施例8

構造式

【0047】

【化19】



で表される化合物。化合物C 45.5 mgと3-ヒドロ

キシメチルベンジルヒドラジン トリフルオロ酢酸塩 67.2 mg を N, N-ジメチルホルムアミド 3 ml に溶解し、飽和炭酸水素ナトリウム水溶液 数滴を加えて、70℃で一晩攪拌した。反応液をメチルエチルケトンに希釈し、希塩酸、水、飽和食塩水で洗浄後、乾燥濃縮した。残渣を分取薄層クロマトグラフィー（展開溶媒；アセトニトリル：テトラヒドロフラン：トルエン：水：酢酸=4：2：2：0.5：0.1）で粗精製後、セファデックス LH-20 のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物 1.6 mg を得た。

Rf 値：0.40（メルク社製、キーゼーゲル 60 F<sub>254</sub>，展開溶媒；アセトニトリル：テトラヒドロフラン：トルエン：水：酢酸=4：2：2：0.5：0.1）

FAB-MS (m/z) : 654 (M<sup>+</sup>)

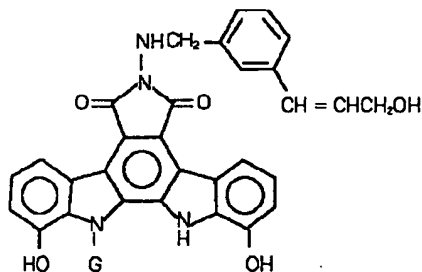
<sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>, δ ppm) : 11.18 (1H, s), 8.86 (1H, d, J=8.4 Hz), 8.78 (1H, d, J=8.7 Hz), 7.42 (1H, s), 7.40 (1H, d, J=7.5 Hz), 7.27 (1H, t, J=7.2 Hz), 7.18 (1H, d, J=7.5 Hz), 7.17 (1H, s), 6.98 (1H, d, J=1.8 Hz), 6.81 (2H, dt, J=1.8, 8.1 Hz), 6.00 (1H, dt, J=1.5, 4.8 Hz), 5.95 (1H, d, J=8.7 Hz), 5.43 (1H, br), 5.16 (2H, br), 4.93 (1H, br), 4.47 (2H, s), 4.25 (1H, d, J=4.8 Hz), 4.10 (1H, br), 4.02 (1H, d, J=10.8 Hz), 3.90 (2H, m), 3.76 (1H, m)

#### 実施例 9

##### 構造式

【0048】

【化 20】



で表される化合物。化合物 D 30 mg と 3-(3-ヒドロキシプロペニル)ベンジルヒドラジン トリフルオロ酢酸塩 40 mg を N, N-ジメチルホルムアミド 1 ml に溶解し、トリエチルアミン 0.5 ml を加えて、80℃で1.5時間攪拌した。反応液を酢酸エチル/メチルエチルケトン混合溶媒に希釈し、希塩酸、飽和食塩水で洗浄後、乾燥濃縮した。残渣を、セファデックス LH

-20 のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮、再びセファデックス LH-20 のクロマト塔にかけエタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物 7.8 mg を得た。

Rf 値：0.48（メルク社製、キーゼーゲル 60 F<sub>254</sub>，展開溶媒；アセトニトリル：テトラヒドロフラン：トルエン：水：酢酸=4：2：2：0.5：0.1）

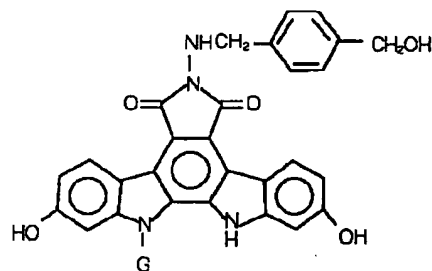
<sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>, δ ppm) : 10.89 (1H, s), 10.35 (1H, br), 9.95 (1H, br), 8.70 (1H, d, J=7.8 Hz), 8.52 (1H, d, J=7.8 Hz), 7.60 (1H, s), 6.91~7.40 (8H, m), 6.53 (1H, d, J=16.2 Hz), 6.39 (1H, td, J=4.6, 16.2 Hz), 6.16 (1H, t, J=5.6 Hz), 5.41 (1H, d, J=5.6 Hz), 5.35 (1H, br), 5.20 (1H, d, J=4.9 Hz), 4.86 (1H, t, J=3.6 Hz), 4.84 (1H, t, J=5.6 Hz), 4.28 (2H, s), 3.89~4.12 (4H, m), 3.30~3.78 (4H, m)

#### 実施例 10

##### 構造式

【0049】

【化 21】



で表される化合物。化合物 C 100 mg と 4-ヒドロキシメチルベンジルヒドラジン塩酸塩 100 mg を N, N-ジメチルホルムアミド 5 ml に溶解し、飽和炭酸水素ナトリウム水溶液 0.5 ml を加えて、室温で1時間、80℃で30分間、攪拌した。反応液をメチルエチルケトンに希釈し、2N塩酸、飽和食塩水で洗浄後、乾燥濃縮した。残渣をセファデックス LH-20 のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物 33 mg を得た。

Rf 値：0.47（メルク社製、キーゼーゲル 60 F<sub>254</sub>，展開溶媒；クロロホルム：メタノール：テトラヒドロフラン=2：1：1）

FAB-MS (m/z) : 655 (M+H)<sup>+</sup>

<sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>, δ ppm) : 11.10 (1H, br), 8.83 (1H,

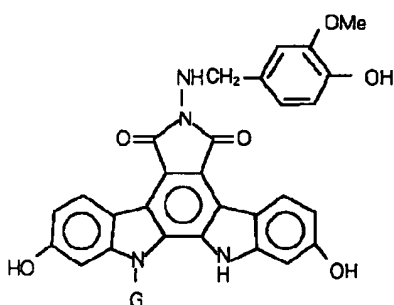
d,  $J=9.3\text{ Hz}$ ), 8.73 (1H, d,  $J=8.4\text{ Hz}$ ), 7.44 (2H, d,  $J=8.4\text{ Hz}$ ), 7.23 (2H, d,  $J=7.8\text{ Hz}$ ), 7.11 (1H, s), 6.94 (1H, s), 6.78 (2H, dt,  $J=9.0, 2.1\text{ Hz}$ ), 6.02 (1H, t,  $J=4.8\text{ Hz}$ ), 5.92 (1H, d,  $J=8.1\text{ Hz}$ ), 4.80~5.23 (2H, br), 4.43 (2H, s), 4.24 (2H, s), 4.03 (1H, m), 3.90 (2H, m), 3.77 (1H, m), 3.50 (2H, m), 3.25~3.42 (3H, m)

#### 実施例 11

##### 構造式

【0050】

【化22】



で表される化合物。化合物C 52mgと3-メトキシ-4-ヒドロキシベンジルヒドラジン塩酸塩 61.4mgをN, N-ジメチルホルムアミド2mlに溶解し、飽和炭酸水素ナトリウム水溶液 0.5mlを加えて、80℃で1時間、攪拌した。反応液を、濃縮乾固した後、残渣をセファデックスLH-20のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物20mgを得た。Rf値: 0.33 (メルク社製、キーゼルゲル60F<sub>254</sub>, 展開溶媒; クロロホルム: メタノール: テトラヒドロフラン=3:1:1)

FAB-MS ( $m/z$ ): ( $M+H$ )<sup>+</sup>

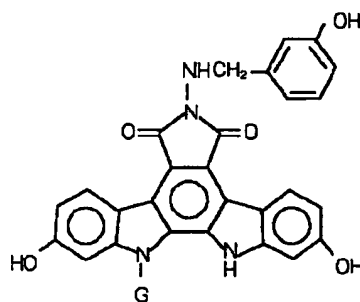
<sup>1</sup>H-NMR (300MHz, DMSO-d<sub>6</sub>,  $\delta$  ppm): 11.12 (1H, s), 9.77 (1H, s), 9.74 (1H, s), 8.86 (1H, s), 8.78 (1H, d,  $J=8.6\text{ Hz}$ ), 8.76 (1H, s), 7.16 (2H, d,  $J=8.1\text{ Hz}$ ), 6.97 (1H, s), 6.70~6.85 (3H, m), 6.64 (1H, d,  $J=8.5\text{ Hz}$ ), 5.86~6.04 (2H, m), 5.85 (1H, t,  $J=3.6\text{ Hz}$ ), 5.32 (1H, d,  $J=3.9\text{ Hz}$ ), 5.10 (1H, d,  $J=4.2\text{ Hz}$ ), 4.90 (1H, d,  $J=4.3\text{ Hz}$ ), 4.11~4.21 (2H, m), 3.86~4.10 (4H, m), 3.77 (3H, m), 3.35~3.52 (2H, m)

#### 実施例 12

##### 構造式

【0051】

【化23】



で表される化合物。化合物C 40mgと3-ヒドロキシベンジルヒドラジン 塩酸塩 31mgをN, N-ジメチルホルムアミド2mlに溶解し、飽和炭酸水素ナトリウム水溶液 0.5mlを加えて、80℃で一晩、攪拌した。反応液を酢酸エチルに希釈し、2N塩酸、飽和炭酸水素ナトリウム水溶液、飽和食塩水で洗浄後、乾燥濃縮した。残渣をセファデックスLH-20のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物17.2mgを得た。

Rf値: 0.24 (メルク社製、キーゼルゲル60F<sub>254</sub>, 展開溶媒; アセトニトリル: テトラヒドロフラン: トルエン: 水: 酢酸=4:2:2:0.5:0.1)

FAB-MS ( $m/z$ ): 641 ( $M+H$ )<sup>+</sup>

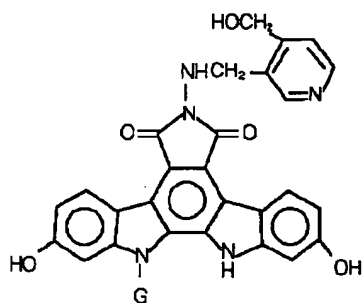
<sup>1</sup>H-NMR (300MHz, DMSO-d<sub>6</sub>,  $\delta$  ppm): 11.18 (1H, s), 9.76 (1H, s), 9.73 (1H, s), 9.28 (1H, s), 8.87 (1H, d,  $J=8.5\text{ Hz}$ ), 8.79 (1H, d,  $J=9.0\text{ Hz}$ ), 7.17 (1H, s), 7.18 (1H, dd,  $J=7.5, 8.0\text{ Hz}$ ), 6.97 (1H, d,  $J=2.3\text{ Hz}$ ), 6.78~6.93 (4H, m), 6.60 (1H, dd,  $J=1.5, 8.0\text{ Hz}$ ), 5.96 (2H, m), 5.85 (1H, m), 5.30 (1H, d,  $J=4.2\text{ Hz}$ ), 5.09 (1H, d,  $J=4.9\text{ Hz}$ ), 4.90 (1H, d,  $J=5.1\text{ Hz}$ ), 4.15 (2H, s), 3.72~4.05 (4H, m), 3.50 (2H, m)

#### 実施例 13

##### 構造式

【0052】

【化24】



で表される化合物。化合物A 43mgと(3-*t*-ブチルジメチルシリルオキシメチル)-3-ピリジナルバルデヒド100mgをメタノール10mlに懸濁し、酢酸18mlを加えて、80℃で一晩攪拌した後に、反応液を濃縮しセファデックスLH-20のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固し、残渣を、メタノール/テトラヒドロフラン(1:1)混合溶媒5mlに溶解し、5%パラジウム炭素を加え、水素気流下室温で3.5時間攪拌した。反応溶液をセライト濾過し、残渣をテトラヒドロフラン5mlに溶解し、過剰量のテトラブチルアンモニウムフルオリド(1.0Mテトラヒドロフラン溶液)を加え、室温で30分間攪拌した。濃縮しセファデックスLH-20のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物4.3mgを得た。

Rf値: 0.1 (メルク社製, キーゼルゲル60 F<sub>254</sub>, 展開溶媒; アセトニトリル: テトラヒドロフラン: トルエン: 水: 酢酸=4:2:2:0.5:0.1)

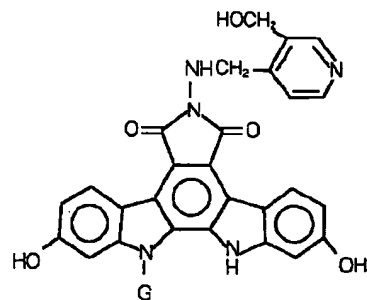
FAB-MS (m/z): 656 (M+H)<sup>+</sup>  
<sup>1</sup>H-NMR (300MHz, DMSO-d<sub>6</sub>, δppm): 11.18 (1H, s), 9.75 (1H, s), 9.73 (1H, s), 8.84 (1H, d, J=8.4Hz), 8.77 (1H, d, J=8.9Hz), 8.42 (1H, d, J=4.9Hz), 8.39 (1H, s), 7.48 (1H, d, J=4.9Hz), 7.17 (1H, d, J=1.1Hz), 6.97 (1H, s), 6.78~6.83 (2H, m), 6.09 (1H, t, J=4.7Hz), 5.97 (1H, d, J=6.6Hz), 5.84 (1H, t, J=3.8Hz), 5.39 (1H, t, J=5.8Hz), 5.30 (1H, d, J=4.8Hz), 5.09 (1H, d, J=4.2Hz), 4.95 (2H, d, J=5.3Hz), 4.90 (1H, d, J=3.3Hz), 4.27 (2H, d, J=4.2Hz), 3.75~4.03 (4H, m), 3.47~3.52 (2H, m)

実施例14

構造式

【0053】

## 【化25】



で表される化合物。化合物A 98mgと4-(3-*t*-ブトキシメチル)ピリジナルバルデヒド92.1mgをメタノール5mlに溶解し、酢酸18mlを加え、80℃で一晩攪拌した後に、反応液を濃縮し、得られた結晶をクロロホルムで洗浄した。これを、メタノール/テトラヒドロフラン(1:1)混合溶媒に溶解し、5%パラジウム炭素を加え水素気流下、3時間攪拌した。セライト濾過、濃縮後、残渣をテトラヒドロフランに溶解し、テトラブチルアンモニウムフルオリドを加え、室温で30分間攪拌した。水を加え、メチルエチルケトンで抽出し、有機層を飽和食塩水で洗浄、濃縮した。セファデックスLH-20のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物13.5mgを得た。Rf値: 0.10 (メルク社製, キーゼルゲル60 F<sub>254</sub>, 展開溶媒; クロロホルム: メタノール: テトラヒドロフラン=2:1:1)

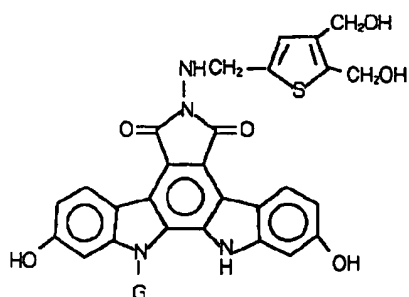
FAB-MS (m/z): 656 (M+H)<sup>+</sup>  
<sup>1</sup>H-NMR (300MHz, DMSO-d<sub>6</sub>, δppm): 11.19 (1H, s), 9.78 (1H, s), 9.75 (1H, s), 8.85 (1H, d, J=9.1Hz), 8.77 (1H, d, J=9.1Hz), 8.51 (1H, s), 8.11 (1H, d, J=5.1Hz), 7.59 (1H, d, J=4.6Hz), 7.17 (1H, d, J=2.1Hz), 6.97 (1H, d, J=1.8Hz), 6.79~6.85 (2H, m), 6.25 (1H, t, J=5.0Hz), 5.98 (1H, d, J=8.3Hz), 5.86 (1H, d, J=4.5Hz), 5.32 (1H, d, J=4.5Hz), 5.23 (1H, t, J=5.6Hz), 5.11 (1H, d, J=4.4Hz), 4.91 (1H, d, J=4.9Hz), 4.74 (2H, d, J=5.2Hz), 4.35 (2H, d, J=7.8Hz), 3.73~4.05 (4H, m), 3.43~3.52 (2H, m)

実施例15

構造式

【0054】

【化26】



で表される化合物。化合物A 50 mg と (4, 5-*tert*-ブチルジメチルシリルオキシメチル) チオフェン-2-カルボキシアルデヒド 100 mg を無水メタノール 10 ml に懸濁し、酢酸 100 ml を加えて、80℃で2時間攪拌した。反応液をセファデックス LH-20 のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固し、中間化合物 40 mg を得た。これをメタノール 3 ml に懸濁し、シアノ水素化ほう素ナトリウム 12 mg、10% 塩酸メタノール溶液 300 ml を加え、室温で1時間攪拌した。反応液を、セファデックス LH-20 のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固し、分取薄層クロマトグラフィ- (メルク社製、キーゼルゲル 60 F 254、展開溶媒; アセトニトリル: テトラヒドロフラン: トルエン: 水: 酢酸 = 4: 2: 2: 0.5: 0.1) により、精製し、表題の式で表される化合物 26 mg を得た。  
Rf 値: 0.28 (メルク社製、キーゼルゲル 60 F 254, 展開溶媒; アセトニトリル: テトラヒドロフラン: トルエン: 水: 酢酸 = 4: 2: 2: 0.5: 0.1)

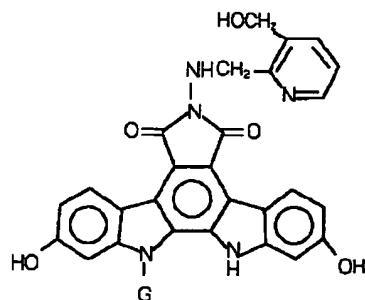
FAB-MS (*m/z*): 690 (*M*<sup>+</sup>)  
<sup>1</sup>H-NMR (300 MHz, DMSO-*d*<sub>6</sub>,  $\delta$  ppm): 11.17 (1H, s), 9.50~10.15 (2H, br), 8.86 (1H, d, *J*=8.4 Hz), 8.78 (1H, d, *J*=8.7 Hz), 7.16 (1H, d, *J*=1.8 Hz), 6.97 (1H, d, *J*=2.1 Hz), 6.92 (1H, s), 6.82 (1H, dd, *J*=1.8, 8.7 Hz), 6.79 (1H, dd, *J*=2.1, 8.4 Hz), 6.04 (1H, t, *J*=5.1 Hz), 6.04 (1H, t, *J*=5.1 Hz), 5.96 (1H, d, *J*=8.1 Hz), 5.88 (1H, br), 5.35 (1H, br), 5.28 (1H, br), 5.15 (1H, br), 4.93 (2H, br), 4.53 (2H, br), 4.73 (2H, d, *J*=4.5 Hz), 4.30 (1H, s), 4.00 (1H, m), 3.91 (2H, m), 3.77 (1H, m), 3.52 (2H, m)

実施例 16

構造式

【0055】

【化 27】



で表される化合物。化合物A 30 mg と 2- (3-*tert*-ブチルジメチルシリルオキシメチル) ピリジルカルバルデヒド 50 mg をメタノール 6 ml に懸濁し、酢酸 30 mm l を加えて、80℃で2時間攪拌した後に、セファデックス LH-20 のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮し、中間化合物 40 mg を得た。これを、テトラヒドロフラン/メタノール (2: 1) の混合溶媒に溶解し、シアノほう素化ナトリウム 15 mg、塩酸メタノール溶液 3 ml を加え、室温で3時間攪拌した。反応溶液を濃縮しセファデックス LH-20 のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物 27 mg を得た。

Rf 値: 0.12 (メルク社製、キーゼルゲル 60 F 254, 展開溶媒; アセトニトリル: テトラヒドロフラン: トルエン: 水: 酢酸 = 4: 2: 2: 0.5: 0.1)

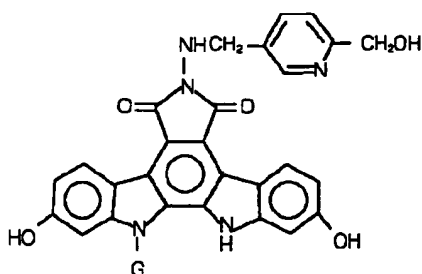
FAB-MS (*m/z*): 656 (*M*+<sup>+</sup>)  
<sup>1</sup>H-NMR (300 MHz, DMSO-*d*<sub>6</sub>,  $\delta$  ppm): 11.18 (1H, br), 9.77 (2H, br), 8.82 (1H, d, *J*=9.0 Hz), 8.784 (1H, d, *J*=9.0 Hz), 8.27 (1H, dd, *J*=1.8, 5.1 Hz), 7.83 (1H, d, *J*=8.1 Hz), 7.28 (1H, dd, *J*=8.1, 5.1 Hz), 7.17 (1H, d, *J*=1.8 Hz), 6.98 (1H, d, *J*=1.8 Hz), 6.82 (1H, dd, *J*=1.8, 9.1 Hz), 6.79 (1H, dd, *J*=1.8, 9.0 Hz), 6.15 (1H, t, *J*=5.1 Hz), 5.97 (1H, d, *J*=8.1 Hz), 5.86 (1H, t, *J*=4.2 Hz), 5.33 (1H, d, *J*=5.4 Hz), 5.31 (1H, d, *J*=5.4 Hz), 5.12 (1H, d, *J*=4.8 Hz), 4.93 (1H, d, *J*=4.5 Hz), 4.87 (2H, d, *J*=6.0 Hz), 4.36 (2H, d, *J*=5.1 Hz), 4.03 (1H, m), 3.91 (2H, s), 3.79 (1H, m), 3.51 (2H, m)

実施例 17

構造式

【0056】

【化28】



で表される化合物。化合物C 30 mg と (6-ヒドロキシメチル-3-ピリジルメチル) ヒドラジン塩酸塩 65 mg をN、N-ジメチルホルムアミド 5 ml に溶解し、トリエチルアミン 0.5 ml を加え、80℃で3時間攪拌した後に、(6-ヒドロキシメチル-3-ピリジルメチル) ヒドラジン塩酸塩 33 mg を加え、80℃で2時間攪拌した。反応液を濃縮乾固後、セファデックス LH-20 のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮し、残渣を再びセファデックス LH-20 のクロマト塔にかけエタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物 7.2 mg を得た。

FAB-MS ( $m/z$ ) : 656 ( $M+H$ )<sup>+</sup>

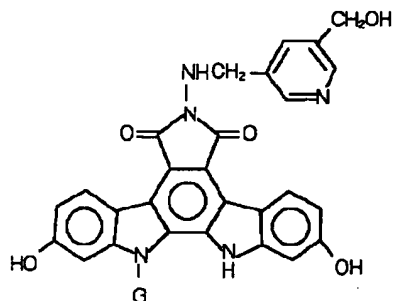
<sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>,  $\delta$  ppm) : 11.12 (1H, br), 8.81 (1H, d,  $J=8.7$  Hz), 8.73 (1H, d,  $J=8.7$  Hz), 8.51 (1H, s), 7.90 (1H, d,  $J=7.9$  Hz), 7.39 (1H, d,  $J=7.9$  Hz), 7.11 (1H, s), 6.93 (1H, s), 6.77 (2H, t,  $J=8.7$  Hz), 6.21 (1H, t,  $J=3.8$  Hz), 5.92 (1H, d,  $J=7.9$  Hz), 4.85~5.50 (5H, br), 4.48 (2H, s), 4.27 (2H, d,  $J=3.8$  Hz), 3.70~4.05 (4H, m), 3.45~3.52 (2H, m)

実施例 18

構造式

【0057】

【化29】



で表される化合物。化合物C 12.5 mg と (5-ヒドロキシメチル-3-ピリジルメチル) ヒドラジン塩酸塩 42 mg をN、N-ジメチルホルムアミド 1 ml に溶解

し、トリエチルアミン 0.1 ml を加えて、80℃で2.5時間攪拌した後に、トリエチルアミン 0.1 ml を加え、50℃で一晩攪拌した。反応液を濃縮乾固後、セファデックス LH-20 のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮し、残渣を再びセファデックス LH-20 のクロマト塔にかけエタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物 2.4 mg を得た。  
Rf 値 : 0.18 (メルク社製, キーゼルゲル 60 F 254, 展開溶媒 ; アセトニトリル : テトラヒドロフラン : トルエン : 水 : 酢酸 = 4 : 2 : 2 : 0.5 : 0.1)

1)

FAB-MS ( $m/z$ ) : 656 ( $M+H$ )<sup>+</sup>

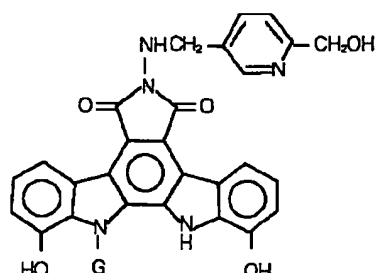
<sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>,  $\delta$  ppm) : 11.18 (1H, br), 9.60~10.02 (2H, br), 8.84 (1H, d,  $J=8.5$  Hz), 8.76 (1H, d,  $J=8.6$  Hz), 8.55 (1H, s), 8.37 (1H, s), 7.84 (1H, s), 7.16 (1H, s), 7.00 (1H, s), 6.75~6.85 (2H, m), 6.21 (1H, t,  $J=4.7$  Hz), 5.95 (1H, d,  $J=7.8$  Hz), 5.88~5.95 (1H, br), 5.40~5.48 (1H, br), 5.26~5.35 (1H, br), 5.15~5.25 (1H, br), 4.90~4.93 (1H, br), 4.56 (2H, d,  $J=4.7$  Hz), 4.50 (2H, s), 3.72~4.05 (4H, m), 3.45~3.55 (2H, m)

実施例 19

構造式

【0058】

【化30】



で表される化合物。化合物D 30 mg と (6-ヒドロキシメチル-3-ピリジルメチル) ヒドラジン塩酸塩 65 mg をN、N-ジメチルホルムアミド 5 ml に溶解し、トリエチルアミン 0.5 ml を加え、80℃で1.5時間攪拌した。反応液を乾燥濃縮後、残渣をセファデックス LH-20 のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物 29 mg を得た。

FAB-MS ( $m/z$ ) : 656 ( $M+H$ )<sup>+</sup>

<sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>,  $\delta$  ppm)



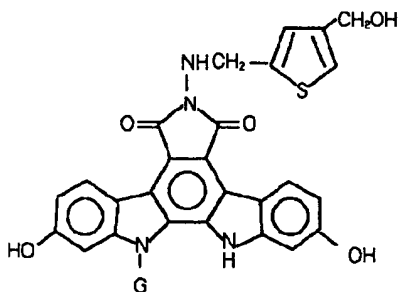
m) : 10.89 (1H, br), 10.36 (1H, br), 9.97 (1H, br), 8.67 (1H, d, J=7.9 Hz), 8.52 (1H, d, J=2.2 Hz), 8.50 (1H, d, J=7.9 Hz), 7.93 (1H, dd, J=2.2, 8.1 Hz), 7.41 (1H, d, J=8.1 Hz), 7.18 (2H, t, J=7.9 Hz), 7.02 (1H, d, J=7.9 Hz), 7.00 (2H, t, J=7.9 Hz), 6.29 (1H, t, J=4.5 Hz), 5.42 (1H, d, J=5.6 Hz), 5.33 (1H, d, J=6.1 Hz), 5.32 (1H, t, J=6.0 Hz), 5.21 (1H, d, J=5.3 Hz), 4.82~4.91 (1H, br), 4.48 (2H, d, J=6.0 Hz), 4.29 (2H, d, J=4.5 Hz), 3.91~4.12 (2H, m), 3.52~3.79 (3H, m), 3.30~3.40 (1H, m)

#### 実施例20

##### 構造式

【0059】

【化31】



で表される化合物。化合物B 30 mgと4-(t-ブチルジメチルシリルオキシエチル)チオフェン-2-カルバルデヒド 152 mgを無水メタノール6 mlに懸濁し、酢酸 30 mlを加えて、80℃で2時間攪拌した。反応液をセファデックスLH-20のクロマト塔にかけメタノールで溶出し、目的物を含む分画を濃縮乾固することにより、中間化合物31 mgを得た。これをメタノール3 mlに懸濁し、シアノ水素化ほう素ナトリウム30 mg、10%塩酸メタノール溶液300 mlを加え、室温で1時間攪拌した。反応液を酢酸エチルで希釈し、水、飽和食塩水で洗浄し、乾燥濃縮した。残渣をセファデックスLH-20のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物5 mgを得た。

Rf値: 0.43 (メルク社製, トルエン: 水: 酢酸 = 4:2:2:0.5:0.1)

FAB-MS (m/z) : 675 (M)<sup>+</sup>

<sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>, δ ppm) : 11.19 (1H, s), 9.80 (2H, br), 8.86 (1H, d, J=9.0 Hz), 8.7

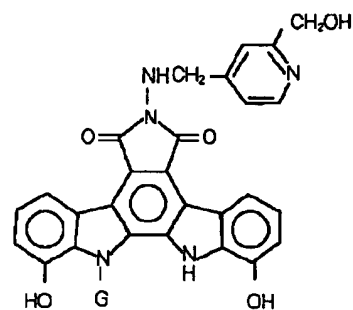
8 (1H, d, J=8.7 Hz), 7.17 (1H, d, J=1.8 Hz), 7.03 (1H, s), 6.98 (1H, d, J=2.1 Hz), 6.95 (1H, s), 6.80 (2H, dt, J=2.1, 8.7 Hz), 6.08 (1H, t, J=5.1 Hz), 5.96 (1H, d, J=7.8 Hz), 5.89 (1H, br), 5.36 (1H, br), 5.13 (1H, br), 4.93 (1H, br), 4.57 (1H, br), 4.38 (2H, d, J=4.2 Hz), 4.05 (2H, m), 3.92 (2H, s), 3.77 (1H, m), 3.50 (5H, m)

#### 実施例21

##### 構造式

【0060】

【化32】



で表される化合物。化合物D 17 mgと4-(2-ヒドロキシメチル-4-ピリジルメチル)ヒドラジン トリフルオロ酢酸塩 12 mgをN, N-ジメチルホルムアミド2 mlに溶解し、トリエチルアミン0.1 mlを加えて、75℃で2時間攪拌した。反応液に水、酢酸エチルを加え水で3回抽出した。水層に食塩を加え、メチルエチルケトンで3回抽出した。有機層を乾燥濃縮後、残渣をセファデックスLH-20のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物8 mgを得た。

FAB-MS (m/z) : 656 (M+H)<sup>+</sup>

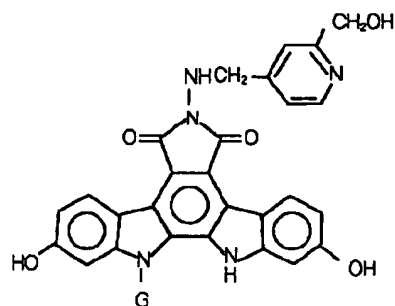
<sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>, δ ppm) : 10.90 (1H, br), 8.66 (1H, d, J=7.6 Hz), 8.50 (1H, d, J=7.6 Hz), 8.41 (1H, d, J=5.0 Hz), 7.57 (1H, s), 7.48 (1H, d, J=5.0 Hz), 7.17 (2H, t, J=7.6 Hz), 7.07 (1H, d, J=7.6 Hz), 7.00 (1H, d, J=7.6 Hz), 6.98 (1H, t, J=7.6 Hz), 6.32 (1H, t, J=4.8 Hz), 5.36 (1H, t, J=3.7 Hz), 5.10~5.50 (4H, br), 4.51 (2H, d, J=3.7 Hz), 4.34 (2H, d, J=4.8 Hz), 3.91~4.12 (2H, m), 3.51~3.80 (3H, m)

#### 実施例22

構造式

【0061】

【化33】



で表される化合物。化合物C 17 mg と (2-ヒドロキシメチル-4-ピリジルメチル) ヒドラジントリフルオロ酢酸塩 12 mg をN, N-ジメチルホルムアミド 1 ml に溶解し、トリエチルアミン 0.1 ml を加えて、80℃で3.5時間攪拌した。反応液に水、酢酸エチルを加えて分液し、水層に食塩を加えメチルエチルケトンで抽出した。有機層を乾燥濃縮後、残渣をセファデックス LH-20 のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物 4 mg を得た。

FAB-MS (m/z) : 656 (M+H<sup>+</sup>)

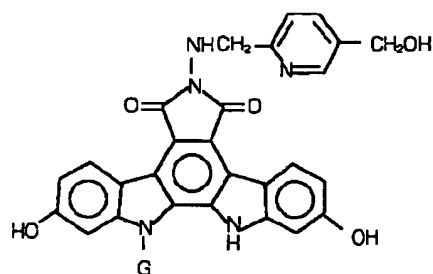
<sup>1</sup>H-NMR (300MHz, DMSO-d<sub>6</sub>, δ ppm) : 11.17 (1H, br), 9.55~10.05 (2H, br), 8.85 (1H, d, J=8.4 Hz), 8.77 (1H, d, J=8.2 Hz), 8.41 (1H, d, J=5.1 Hz), 7.56 (1H, s), 7.47 (1H, d, J=5.1 Hz), 7.15 (1H, s), 6.96 (1H, s), 6.72~6.85 (2H, m), 6.26 (1H, t, J=4.9 Hz), 5.94 (1H, d, J=8.6 Hz), 5.80~5.99 (1H, br), 5.30~5.42 (2H, br), 5.10~5.20 (1H, br), 4.85~4.95 (1H, br), 4.51 (2H, d, J=1.8 Hz), 4.32 (2H, d, J=4.5 Hz), 3.89~4.04 (1H, m), 3.90 (2H, m), 3.74~3.78 (1H, m), 3.50 (2H, m)

実施例 23

構造式

【0062】

【化34】



で表される化合物。化合物A 14 mg と 5-tert-ブチルジメチルシリルオキシメチルピリジン-2-カルバルデヒド 14.7 mg を無水メタノール 2 ml に懸濁し、酢酸 8 ml を加えて、80℃で一晩攪拌した。反応液セファデックス LH-20 のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固し、中間化合物 15.3 mg を得た。シアノ水素化ほう素ナトリウム 75 mg をテトラヒドロフラン 1 ml に懸濁し、塩化亜鉛 (1.0 M ジエチルエーテル溶液) 0.55 ml を滴下した。中間化合物 15.3 mg を、テトラヒドロフラン 3 ml に懸濁して加え、室温で2.5時間攪拌した。反応液に飽和水炭酸水素ナトリウム水溶液を加え、メチルエチルケトンで抽出した。有機層を乾燥濃縮後、残渣をテトラヒドロフラン 3 ml に溶解し、過剰量のテトラブチルアンモニウムフルオリド (1 M テトラヒドロフラン溶液) を0℃で滴下した。室温で30分間攪拌後、水を加え、メチルエチルケトンで抽出した。有機層を乾燥濃縮後、残渣をセファデックス LH-20 のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物 4.5 mg を得た。

Rf 値: 0.1 (メルク社製, キーゼルゲル 60

F<sub>254</sub>, 展開溶媒; クロロホルム: メタノール: テトラヒドロフラン = 3:1:1)

FAB-MS (m/z) : 656 (M+H)<sup>+</sup>

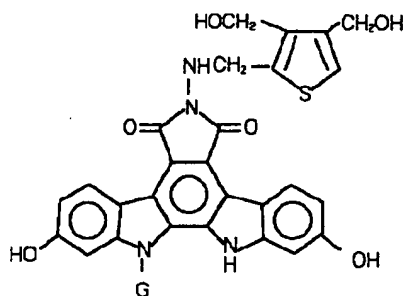
<sup>1</sup>H-NMR (300MHz, DMSO-d<sub>6</sub>, δ ppm) : 11.18 (1H, s), 9.77 (2H, br), 8.84 (1H, d, J=8.5 Hz), 8.76 (1H, d, J=8.6 Hz), 8.35 (1H, d, J=1.7 Hz), 7.72 (2H, s), 7.17 (1H, d, J=1.7 Hz), 6.98 (1H, d, J=1.9 Hz), 6.78~6.98 (2H, m), 6.22 (1H, t, J=4.6 Hz), 5.96 (1H, d, J=8.9 Hz), 5.87 (1H, br), 5.35 (1H, br), 5.22 (1H, t, J=2.0 Hz), 5.11 (1H, br), 4.91 (1H, br), 4.46 (2H, d, J=4.2 Hz), 4.35 (2H, d, J=4.6 Hz), 3.73~4.09 (4H, m), 3.49 (2H, s)

実施例 24

構造式

【0063】

## 【化35】



で表される化合物。化合物A 30 mgと3, 4-ビス-(*t*-ブチルジメチルシリルオキシメチル)チオフェン-2-カルバルデヒド 30 mgを無水メタノール 6 mlに懸濁し、酢酸 30 mlを加えて、80℃で2時間攪拌した。反応液をセファデックス LH-20のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固し、中間化合物 31 mgを得た。これを、メタノール 5 mlに懸濁し、シアノ水素化ほう素ナトリウム 10 mg、10%塩酸メタノール溶液 100 mlを加え、室温で30分間攪拌した。反応液を酢酸エチルに希釈し、水、飽和食塩水で洗浄した。有機層を乾燥濃縮後、残渣をセファデックス LH-20のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物 25 mgを得た。R<sub>f</sub>値：0.30 (メルク社製、キーゼルゲル 60 F<sub>254</sub>, 展開溶媒；アセトニトリル：テトラヒドロフラン：トルエン：水：酢酸=4：2：2：0.5：0.1)

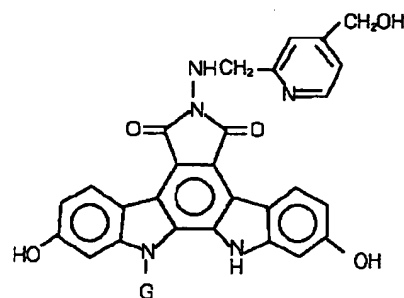
FAB-MS (*m/z*) : 691 (M+H)<sup>+</sup>  
<sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>, δ ppm) : 11.19 (1H, s), 9.79 (1H, s), 9.76 (1H, s), 8.86 (1H, d, J=8.4 Hz), 8.78 (1H, d, J=8.7 Hz), 7.18 (1H, d, J=1.8 Hz), 7.15 (1H, s), 6.98 (1H, d, J=2.1 Hz), 6.82 (2H, dt, J=8.7, 1.8 Hz), 6.04 (1H, t, J=5.4 Hz), 5.97 (1H, d, J=8.1 Hz), 5.86 (1H, t, J=3.6 Hz), 5.33 (1H, d, J=4.2 Hz), 5.12 (1H, d, J=4.2 Hz), 5.01 (1H, t, J=6.0 Hz), 4.93 (1H, d, J=4.8 Hz), 4.85 (1H, t, J=5.7 Hz), 4.52 (2H, d, J=5.7 Hz), 4.70 (2H, d, J=5.7 Hz), 4.40 (2H, d, J=4.8 Hz), 4.01 (1H, m), 3.92 (2H, m), 3.77 (1H, m), 3.50 (2H, m)

## 実施例 25

## 構造式

【0064】

## 【化36】



で表される化合物。化合物A 18 mgと4-ヒドロキシメチルピリジン-2-カルバルデヒド 7 mgを無水メタノール 2 mlに懸濁し、酢酸 数滴を加えて、80℃で1.5時間攪拌した。反応液を濃縮乾固後、セファデックス LH-20のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固し、中間化合物 22 mgを得た。シアノ水素化ほう素ナトリウム 90 mgをテトラヒドロフラン 1 mlに懸濁し、塩化亜鉛 (1.0 Mジエチルエーテル溶液) 0.66 mlを滴下した。中間化合物 22 mgを、テトラヒドロフラン 3 mlに懸濁して加え、室温で2.5時間攪拌した。反応液に水を加え、飽和炭酸水素ナトリウム水溶液で弱アルカリ性にし、酢酸エチルで抽出した。有機層を乾燥濃縮後、残渣をセファデックス LH-20のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物 11 mgを得た。

FAB-MS (*m/z*) : 656 (M+H)<sup>+</sup>  
<sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>, δ ppm) : 11.21 (1H, s), 9.80 (1H, s), 9.77 (1H, s), 8.86 (1H, d, J=8.6 Hz), 8.78 (1H, d, J=8.1 Hz), 7.82~7.95 (1H, m), 7.68~7.75 (1H, m), 7.33~7.43 (1H, m), 7.19 (1H, s), 7.00 (1H, s), 6.78~6.89 (2H, m), 6.22 (1H, t, J=4.5 Hz), 5.97 (1H, d, J=7.9 Hz), 5.86 (1H, t, J=3.8 Hz), 5.33 (1H, d, J=4.2 Hz), 5.29 (1H, t, J=5.9 Hz), 5.11 (1H, d, J=5.0 Hz), 4.91 (1H, d, J=4.1 Hz), 4.42 (2H, d, J=5.5 Hz), 4.33 (2H, d, J=1.6 Hz), 3.99~4.09 (1H, m), 3.91 (2H, m), 3.72~3.80 (1H, m), 3.50 (2H, m)

## 実施例 26

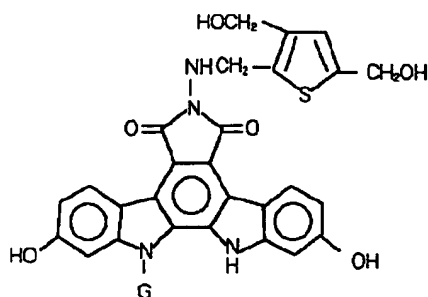
## 構造式

【0065】

【化37】



## 【化39】



で表される化合物。化合物A 40mgと3, 5-ビス-(*t*-ブチルジメチルシリルオキシメチル)チオフェン-2-カルバルデヒド60mgを無水メタノール8mlに懸濁し、酢酸 40mlを加えて、80℃で2時間攪拌した。反応液をセファデックスLH-20のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固し、中間化合物 46mgを得た。これをメタノール5mlに懸濁し、シアノ水素化ほう素ナトリウム30mg、10%塩酸メタノール溶液300mlを加え、室温で30分間攪拌した。反応液を酢酸エチルで希釈し、水、飽和食塩水で洗浄した。有機層を乾燥濃縮後、残渣をセファデックスLH-20のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物36mgを得た。

Rf値: 0.24 (メルク社製, キーゼルゲル60F<sub>254</sub>, 展開溶媒; アセトニトリル: テトラヒドロフラン: トルエン: 水: 酢酸=4:2:2:0.5:0.1)

FAB-MS (m/z): 690 (M)<sup>+</sup>

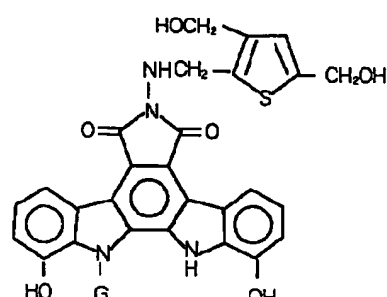
<sup>1</sup>H-NMR (300MHz, DMSO-d<sub>6</sub>, δppm): 11.19 (1H, s), 9.79 (1H, s), 9.76 (1H, s), 8.86 (1H, d, J=8.4Hz), 8.78 (1H, d, J=8.4Hz), 7.18 (1H, d, J=1.8Hz), 6.98 (1H, d, J=1.8Hz), 6.83 (1H, s), 6.82 (2H, dt, J=1.8, 8.4Hz), 5.99 (1H, t, J=4.8Hz), 5.97 (1H, d, J=9.0Hz), 5.87 (1H, t, J=4.2Hz), 5.35 (1H, t, J=5.4Hz), 5.33 (1H, d, J=4.8Hz), 5.12 (1H, d, J=5.1Hz), 4.96 (1H, d, J=5.7Hz), 4.94 (1H, d, J=5.4Hz), 4.49 (4H, t, J=6.6Hz), 4.34 (2H, d, J=4.8Hz), 4.03 (1H, m), 3.92 (2H, m), 3.77 (1H, m), 3.50 (2H, m)

実施例29

構造式

【0068】

## 【化40】



で表される化合物。化合物B 50mgと3, 5-ビス-(*t*-ブチルジメチルシリルオキシメチル)チオフェン-2-カルバルデヒド60mgを無水メタノール/N,N-ジメチルホルムアミド(5:1)12mlに溶解し、酢酸50mlを加えて、80℃で一晩攪拌した。反応液を酢酸エチルで希釈し、水、飽和食塩水で洗浄後、乾燥濃縮した。残渣をセファデックスLH-20のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固し、残渣をテトラヒドロフラン/メタノール混合溶媒(2:1)6mlに溶解し、シアノ水素化ほう素ナトリウム30mg、10%塩酸メタノール溶液300mlを加え、室温で1時間攪拌した。反応液を酢酸エチルで希釈し、飽和炭酸水素ナトリウム水溶液、飽和食塩水で洗浄した。有機層を乾燥濃縮後、残渣をセファデックスLH-20のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物37mgを得た。

Rf値: 0.31 (メルク社製, キーゼルゲル60F<sub>254</sub>, 展開溶媒; アセトニトリル: テトラヒドロフラン: トルエン: 水: 酢酸=4:2:2:0.5:0.1)

FAB-MS (m/z): 690 (M)<sup>+</sup>

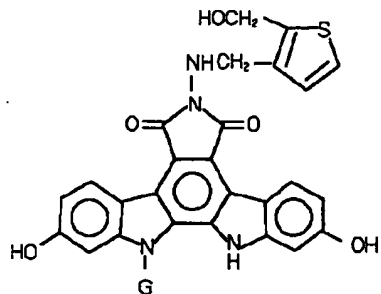
<sup>1</sup>H-NMR (300MHz, DMSO-d<sub>6</sub>, δppm): 10.90 (1H, s), 10.37 (1H, br), 9.98 (1H, br), 8.69 (1H, d, J=8.4Hz), 8.52 (1H, d, J=8.4Hz), 7.19 (2H, dt, J=1.5, 8.4Hz), 7.05 (1H, d, J=8.6Hz), 7.01 (2H, t, J=8.4Hz), 6.83 (1H, s), 6.04 (1H, t, J=4.8Hz), 5.42 (1H, d, J=5.7Hz), 5.35 (2H, t, J=6.0Hz), 5.21 (1H, d, J=5.4Hz), 4.95 (1H, t, J=6.0Hz), 4.91 (1H, br), 4.50 (4H, t, J=5.7Hz), 4.36 (2H, d, J=5.4Hz), 4.00 (2H, m), 3.73 (1H, m), 3.62 (2H, m), 3.40 (1H, m)

実施例30

構造式

【0069】

【化41】



で表される化合物。化合物A 20 mgと2-ヒドロキシメチルチオフェン-3-カルバルデヒド 20 mgを無水メタノール4 mlに溶解し、酢酸20 mlを加えて、80℃で2時間攪拌した。反応液を減圧濃縮後、残渣をセファデックスLH-20のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固し、残渣をテトラヒドロフラン/メタノール混合溶媒(2:1) 3 mlに溶解し、シアノ水素化ほう素ナトリウム30 mg、10%塩酸メタノール溶液300 mlを加え、室温で30分間攪拌した。反応液を減圧濃縮後、残渣をセファデックスLH-20のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物16 mgを得た。

Rf値: 0.49 (メルク社製、キーゼーゲル60F<sub>254</sub>, 展開溶媒; アセトニトリル: テトラヒドロフラン: トルエン: 水: 酢酸=4:2:2:0.5:0.1)

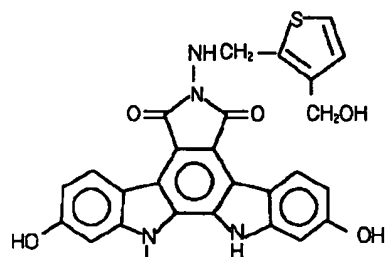
FAB-MS (m/z): 660 (M)<sup>+</sup>  
<sup>1</sup>H-NMR (300MHz, DMSO-d<sub>6</sub>, δ ppm): 11.18 (1H, s), 9.79 (1H, s), 9.75 (1H, s), 8.86 (1H, d, J=8.4Hz), 8.78 (1H, d, J=8.4Hz), 7.30 (1H, d, J=4.8Hz), 7.17 (1H, d, J=2.1Hz), 7.09 (1H, d, J=5.4Hz), 6.98 (1H, d, J=2.1Hz), 6.82 (1H, dd, J=2.1, 8.4Hz), 6.80 (1H, dd, J=2.1, 8.4Hz), 5.97 (1H, d, J=8.1Hz), 5.92 (1H, t, J=5.1Hz), 5.86 (1H, t, J=3.9Hz), 5.37 (1H, d, J=5.7Hz), 5.33 (1H, d, J=4.5Hz), 5.12 (1H, d, J=4.8Hz), 4.93 (1H, d, J=4.8Hz), 4.76 (2H, d, J=5.7Hz), 4.20 (2H, d, J=5.1Hz), 4.00 (1H, m), 3.91 (2H, s), 3.77 (1H, m), 3.50 (2H, m)

実施例31

構造式

【0070】

【化42】



で表される化合物。化合物A 30 mgと3-tert-ブチルジメチルシリルオキシメチルチオフェン-2-カルバルデヒド30 mgを無水メタノール5 mlに溶解し、酢酸30 mlを加えて、80℃で2時間攪拌した。反応液を減圧濃縮後、残渣をセファデックスLH-20のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固し、残渣をメタノール3 mlに懸濁し、シアノ水素化ほう素ナトリウム30 mg、10%塩酸メタノール溶液300 mlを加え、室温で1時間攪拌した。反応液をセファデックスLH-20のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物24 mgを得た。  
Rf値: 0.40 (メルク社製、キーゼーゲル60F<sub>254</sub>, 展開溶媒; アセトニトリル: テトラヒドロフラン: トルエン: 水: 酢酸=4:2:2:0.5:0.1)

FAB-MS (m/z): 660 (M)<sup>+</sup>

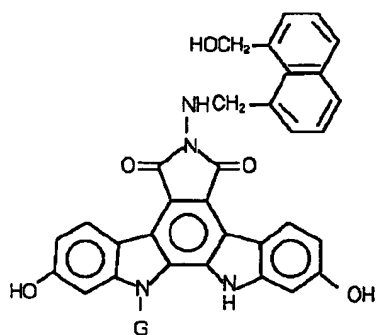
<sup>1</sup>H-NMR (300MHz, DMSO-d<sub>6</sub>, δ ppm): 11.19 (1H, s), 9.78 (1H, s), 9.75 (1H, s), 8.85 (1H, d, J=8.7Hz), 8.78 (1H, d, J=9.0Hz), 7.31 (1H, d, J=4.8Hz), 7.18 (1H, d, J=1.8Hz), 6.99 (1H, d, J=4.8Hz), 6.97 (1H, d, J=1.8Hz), 6.81 (2H, dd, J=1.8, 9.0Hz), 6.06 (1H, t, J=4.8Hz), 5.97 (1H, d, J=8.7Hz), 5.86 (1H, t, J=3.9Hz), 5.33 (1H, d, J=4.5Hz), 5.12 (1H, d, J=4.5Hz), 4.99 (1H, t, J=5.4Hz), 4.93 (1H, d, J=5.1Hz), 4.53 (2H, d, J=5.7Hz), 4.38 (2H, d, J=4.8Hz), 4.02 (1H, m), 3.91 (2H, m), 3.77 (1H, m), 3.50 (2H, m)

実施例32

構造式

【0071】

【化43】



で表される化合物。化合物A 35mgと8-*t*-ブチルジメチルシリルオキシメチルー1-ナフトアルデヒド60mgをメタノール2mlに懸濁し、酢酸を数滴加え、60℃で2時間攪拌した。反応液を濃縮し、得られた固体をクロロフォルムで洗浄し、中間化合物 32.5mgを得た。シアノ水素化ほう素ナトリウム 68mgをテトラヒドロフラン3mlに懸濁し、塩化亜鉛(1.0Mジエチルエーテル溶液) 0.5mlを滴下した。中間化合物32.5mgをテトラヒドロフラン2mlに懸濁して加え、室温で2時間攪拌後、飽和食塩水を加え、酢酸エチル/メチルエチルケトンの混合溶媒で抽出した。有機層を乾燥濃縮し、残渣をテトラヒドロフラン1.5mlに溶解し、テトラブチルアンモニウム フロリド 0.5mlを加えた。室温で1.5時間攪拌後、酢酸エチル/メチルエチルケトンの混合溶媒で希釈し、水、飽和食塩水で洗浄し、有機層を乾燥濃縮し、セファデックスLH-20のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物3.3mgを得た。

FAB-MS ( $m/z$ ) : 705 ( $M+H$ )<sup>+</sup>

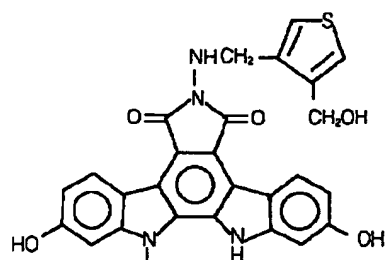
<sup>1</sup>H-NMR (300MHz, DMSO-*d*<sub>6</sub>,  $\delta$  ppm) : 11.16 (1H, s), 8.84 (1H, d,  $J=7.9$ Hz), 8.76 (1H, d,  $J=7.9$ Hz), 7.87 (2H, d,  $J=7.4$ Hz), 7.68 (1H, d,  $J=7.4$ Hz), 7.58 (1H, d,  $J=7.4$ Hz), 7.49 (1H, d,  $J=7.4$ Hz), 7.39 (1H, t,  $J=7.4$ Hz), 7.15 (1H, s), 6.97 (1H, s), 6.80 (2H, t,  $J=7.9$ Hz), 5.86~6.00 (3H, m), 5.42 (2H, s), 4.85 (2H, d,  $J=4.2$ Hz), 4.80~5.50 (4H, br), 3.72~4.05 (4H, m), 3.45~3.59 (2H, m)

実施例33

構造式

【0072】

【化44】



で表される化合物。化合物A 30mgと4-*t*-ブチルジメチルシリルオキシチオフエン-3-カルバルデヒド30mgをメタノール6mlに懸濁し、酢酸30mlを加え、80℃で2時間攪拌した。反応液をセファデックスLH-20のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固し、これを、テトラヒドロフラン/メタノール混合溶媒(2:1) 5mlに溶解し、シアノ水素化ほう素ナトリウム 20mg、10%塩酸メタノール溶液200mlを加え、室温で30分間攪拌した。反応液を酢酸エチルで希釈し、水、飽和食塩水で洗浄し、乾燥濃縮した。残渣をセファデックスLH-20のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物15mgを得た。

Rf値: 0.47 (メルク社製, キーゼルゲル60F

254, 展開溶媒; アセトニトリル: テトラヒドロフラン: トルエン: 水: 酢酸=4:2:2:0.5:0.

1)

FAB-MS ( $m/z$ ) : 661 ( $M+H$ )<sup>+</sup>

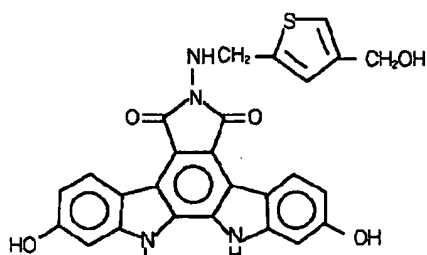
<sup>1</sup>H-NMR (300MHz, DMSO-*d*<sub>6</sub>,  $\delta$  ppm) : 11.19 (1H, s), 9.79 (1H, s), 9.76 (1H, s), 8.86 (1H, d,  $J=8.7$ Hz), 8.78 (1H, d,  $J=8.7$ Hz), 7.43 (1H, d,  $J=3.3$ Hz), 7.30 (1H, d,  $J=3.6$ Hz), 7.17 (1H, d,  $J=2.1$ Hz), 6.98 (1H, d,  $J=2.1$ Hz), 6.83 (1H, dd,  $J=2.1, 8.7$ Hz), 6.81 (1H, dd,  $J=2.1, 8.7$ Hz), 6.04 (1H, t,  $J=5.1$ Hz), 5.97 (1H, d,  $J=9.0$ Hz), 5.87 (1H, t,  $J=3.6$ Hz), 5.34 (1H, d,  $J=3.9$ Hz), 5.12 (1H, d,  $J=5.1$ Hz), 5.10 (1H, t,  $J=5.1$ Hz), 4.92 (1H, d,  $J=4.5$ Hz), 4.67 (2H, d,  $J=5.4$ Hz), 4.23 (2H, d,  $J=4.2$ Hz), 4.01 (1H, m), 3.92 (2H, s), 3.77 (1H, m), 3.50 (2H, m)

実施例34

構造式

【0073】

【化45】



で表される化合物。化合物A 38 mgと4-ヒドロキシメチルチオフェン-2-カルバルデヒド 25 mgを無水メタノール7 mlに懸濁し、酢酸45 mlを加えて、80℃で7時間攪拌した。反応液を減圧濃縮後、メタノール/クロロホルムから結晶38 mgを濾取した。この結晶をテトラヒドロフラン/メタノール(4:1) 10 mlに溶解し、シアノ水素化ほう素ナトリウム13 mg、10%塩酸メタノール溶液0.5 mlを加え、室温で30分間攪拌した。酢酸エチルに希釈し、飽和食塩水で洗浄後、乾燥濃縮した。残渣をセファデックスLH-20のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物21.7 mgを得た。

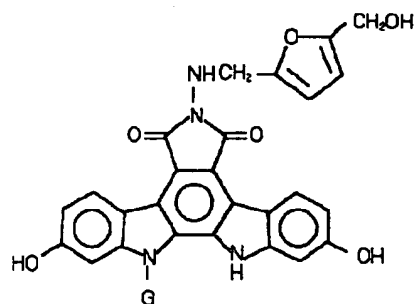
Rf値: 0.24 (メルク社製、キーゼルゲル60 F<sub>254</sub>, 展開溶媒; アセトニトリル: テトラヒドロフラン: トルエン: 水: 酢酸=4:2:2:0.5:0.1)

FAB-MS (m/z): 660 (M<sup>+</sup>)  
<sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>, δ ppm): 11.19 (1H, s), 9.77 (2H, br), 8.86 (1H, d, J=8.6 Hz), 8.78 (1H, d, J=8.6 Hz), 7.17 (1H, s), 7.14 (1H, d, J=1.8 Hz), 6.98 (2H, m), 6.81 (2H, dt, J=1.8, 6.9 Hz), 6.12 (1H, t, J=5.1 Hz), 5.97 (1H, d, J=8.1 Hz), 5.87 (1H, s), 5.35 (1H, d, J=1.8 Hz), 5.13 (1H, d, J=2.4 Hz), 5.01 (1H, t, J=5.4 Hz), 4.93 (1H, d, J=3.6 Hz), 4.40 (2H, d, J=4.5 Hz), 4.34 (2H, d, J=4.8 Hz), 4.00 (1H, dd, J=2.1, 11.6 Hz), 3.91 (2H, s), 3.79 (1H, m), 3.51 (2H, br)

#### 実施例35

##### 構造式

【0074】  
 【化46】



で表される化合物。化合物A 107 mgと5-ヒドロキシメチルフルフラール126 mgをメタノール2 mlに懸濁し、酢酸を数滴加え、80℃で一晩攪拌した。反応液を濃縮し、得られた固体をクロロホルムで洗浄した。これを、メタノール/テトラヒドロフラン混合溶媒(1:2) 5 mlに溶解し、シアノ水素化ほう素ナトリウム 62.8 mg、10%塩酸メタノール溶液5 mlを加え、室温で30分間攪拌した。反応液を酢酸エチル/メチルエチルケトンの混合溶媒で希釈し、水、飽和食塩水で洗浄した。有機層を乾燥濃縮し、セファデックスLH-20のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物103 mgを得た。

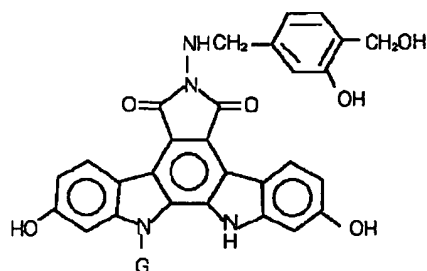
FAB-MS (m/z): 644 (M<sup>+</sup>)

<sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>, δ ppm): 11.19 (1H, s), 9.77 (2H, br), 8.85 (1H, d, J=8.5 Hz), 8.77 (1H, d, J=8.6 Hz), 7.18 (1H, d, J=2.1 Hz), 6.98 (1H, d, J=1.7 Hz), 6.75~6.86 (2H, m), 6.31 (1H, d, J=3.1 Hz), 6.15 (1H, d, J=3.1 Hz), 6.03 (1H, t, J=4.7 Hz), 5.97 (1H, d, J=8.3 Hz), 5.87 (1H, t, J=3.6 Hz), 5.34 (1H, d, J=3.9 Hz), 5.08~5.15 (2H, m), 4.93 (1H, d, J=4.5 Hz), 4.28 (2H, d, J=5.6 Hz), 4.20 (2H, d, J=4.7 Hz), 3.72~4.05 (4H, m), 3.45~3.55 (2H, m)

#### 実施例36

##### 構造式

【0075】  
 【化47】





で表される化合物。化合物A 39 mgと3-ヒドロキシ-4-ヒドロキシメチルベンズアルデヒド 33 mgをメタノール8 mlに懸濁し、酢酸150  $\mu$ lを加え、室温で3晩攪拌した。反応液を濾過し、得られた固体をクロロホルムで洗浄した。これを、メタノール/テトラヒドロフラン混合溶媒(1:2) 5 mlに溶解し、シアノ水素化ほう素ナトリウム 9 mg、10%塩酸メタノール溶液 数滴を加え、室温で1時間攪拌した。反応液を減圧乾固し、セファデックスLH-20のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物3.5 mgを得た。

FAB-MS ( $m/z$ ) : 670 ( $M^+$ )

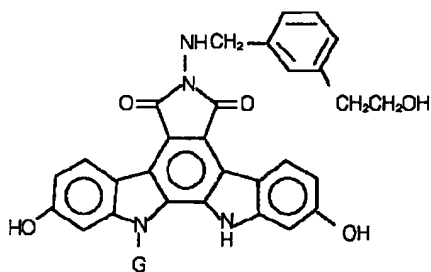
$^1\text{H-NMR}$  (300 MHz, DMSO- $d_6$ ,  $\delta$  ppm) : 11.18 (1H, s), 9.77 (1H, s), 9.76 (1H, s), 9.28 (1H, br), 8.87 (1H, d,  $J=8.5$  Hz), 8.78 (1H, d,  $J=8.5$  Hz), 7.18 (1H, d,  $J=7.9$  Hz), 7.17 (1H, s), 6.97 (1H, d,  $J=2.0$  Hz), 6.77~6.93 (4H, m), 5.96 (1H, d,  $J=8.2$  Hz), 5.92 (1H, t,  $J=5.0$  Hz), 5.86 (1H, t,  $J=3.2$  Hz), 5.33 (1H, d,  $J=4.3$  Hz), 5.12 (1H, d,  $J=4.6$  Hz), 4.92 (1H, d,  $J=5.0$  Hz), 5.83 (1H, br), 4.41 (2H, d,  $J=3.2$  Hz), 4.14 (2H, d,  $J=5.0$  Hz), 4.00 (1H, m), 3.90 (2H, m), 3.78 (1H, m), 3.50 (2H, m)

#### 実施例37

##### 構造式

【0076】

【化48】



で表される化合物。化合物A 30 mgと3-(2-ヒドロキシエチル)ベンズアルデヒド 24.9 mgをメタノール1 mlに懸濁し、酢酸を数滴加え、80℃で1時間攪拌した。反応液を減圧濃縮後、残渣をクロロホルムで洗浄した。これを、メタノール2 mlに懸濁し、シアノ水素化ほう素ナトリウム 9.0 mg、10%塩酸メタノール溶液 数滴を加え、室温で30分間攪拌した。反応液を減圧乾固した残渣をセファデックスLH-20のクロマト塔にかけメタノールで溶出した。目的物を含む

分画を濃縮乾固することにより、表題の式で表される化合物20.7 mgを得た。

FAB-MS ( $m/z$ ) : 669 ( $M+H$ ) $^+$

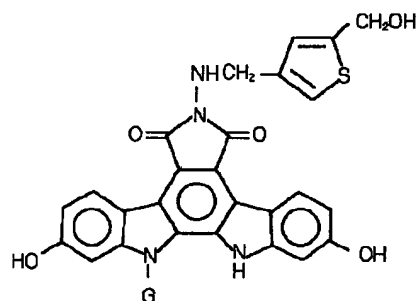
$^1\text{H-NMR}$  (300 MHz, DMSO- $d_6$ ,  $\delta$  ppm) : 11.18 (1H, s), 9.78 (1H, s), 9.75 (1H, s), 8.87 (1H, d,  $J=8.5$  Hz), 8.79 (1H, d,  $J=8.6$  Hz), 7.36 (1H, s), 7.32 (1H, d,  $J=7.6$  Hz), 7.15~7.25 (2H, m), 7.07 (1H, d,  $J=7.6$  Hz), 6.97 (1H, d,  $J=2.0$  Hz), 6.75~6.85 (2H, m), 6.02 (1H, d,  $J=5.2$  Hz), 5.96 (1H, d,  $J=8.2$  Hz), 5.86 (1H, t,  $J=3.3$  Hz), 5.33 (1H, d,  $J=4.3$  Hz), 5.11 (1H, d,  $J=4.9$  Hz), 4.90 (1H, d,  $J=5.4$  Hz), 4.61 (1H, t,  $J=5.3$  Hz), 4.23 (2H, d,  $J=4.5$  Hz), 3.72~4.05 (4H, m), 3.45~3.60 (4H, m), 2.69 (2H, t,  $J=7.3$  Hz)

#### 実施例38

##### 構造式

【0077】

【化49】



で表される化合物。化合物A 40 mgと5-ヒドロキシメチルチオフェン-3-カルバルデヒド 40 mgをメタノール8 mlに懸濁し、酢酸40 mlを加え、80℃で3時間攪拌した。反応液を室温に冷却し、クロロホルムを加え、粉体を濾取した。これを、メタノール5 mlに懸濁し、シアノ水素化ほう素ナトリウム20 mg、10%塩酸メタノール溶液200 mlを加え、室温で30分間攪拌した。反応液を酢酸エチル/メチルエチルケトンの混合溶媒で希釈し、水、飽和食塩水で洗浄し、乾燥濃縮した。残渣をセファデックスLH-20のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物21 mgを得た。

Rf値: 0.29 (メルク社製, キーゼルゲル60 F<sub>254</sub>, 展開溶媒; アセトニトリル: テトラヒドロフラン: トルエン: 水: 酢酸=4:2:2:0.5:0.1)

FAB-MS (m/z) : 660 (M<sup>+</sup>)

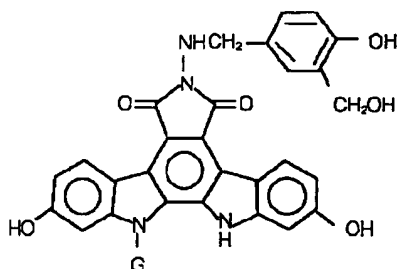
<sup>1</sup>H-NMR (300MHz, DMSO-d<sub>6</sub>, δppm) : 11.19 (1H, s), 9.80 (2H, br), 8.86 (1H, d, J=9.0Hz), 8.79 (1H, d, J=8.7Hz), 7.34 (1H, s), 7.17 (1H, d, J=1.5Hz), 7.04 (1H, s), 6.97 (1H, d, J=1.5Hz), 6.82 (1H, dd, J=1.5, 9.0Hz), 6.80 (1H, dd, J=8.7, 1.5Hz), 5.97 (2H, t, J=5.1Hz), 5.87 (1H, br), 5.40 (1H, t, J=6.0Hz), 5.35 (1H, br), 5.13 (1H, s), 4.91 (1H, d, J=3.9Hz), 4.57 (2H, d, J=4.2Hz), 4.20 (2H, d, J=4.8Hz), 3.88~4.10 (3H, m), 3.78 (1H, m), 3.50 (2H, m)

実施例39

構造式

【0078】

【化50】



で表される化合物。化合物A 38mgと3-ヒドロキシメチル-4-ヒドロキシベンズアルデヒド91mgをN, N-ジメチルホルムアミド2mlに溶解し、酢酸3滴を加え、80℃で3時間攪拌した。反応液を減圧濃縮

後、残渣をクロロホルムで洗浄した。これを、メタノール3mlに懸濁し、シアノ水素化ほう素ナトリウム 40mg、10%塩酸メタノール溶液数滴を加え、室温で30分間攪拌した。反応液をセファデックスLH-20のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物8.9mgを得た。

Rf値: 0.15 (メルク社製, キーゼルゲル60F<sub>254</sub>, 展開溶媒; アセトニトリル: テトラヒドロフラン: トルエン: 水: 酢酸=4:2:2:0.5:0.1)

FAB-MS (m/z) :

<sup>1</sup>H-NMR (300MHz, DMSO-d<sub>6</sub>, δppm) : 11.19 (1H, s), 9.75 (1H, br), 9.74 (1H, br), 9.23 (1H, br), 8.87 (1H, d, J=8.6Hz), 8.79 (1H, d, J=8.6Hz), 7.37 (1H, s), 7.12~7.20 (2H, m), 6.98 (1H, d, J=2.1Hz), 6.75~6.85 (2H, m), 6.70 (1H, d, J=8.3Hz), 5.97 (1H, d, J=8.3Hz), 5.86 (1H, t, J=4.4Hz), 5.76 (1H, t, J=5.3Hz), 5.33 (1H, d, J=4.4Hz), 5.10 (1H, d, J=3.4Hz), 4.89~4.98 (2H, m), 4.44 (2H, d, J=4.5Hz), 3.72~4.15 (6H, m), 3.48~3.55 (2H, m)

【0079】

【発明の効果】本発明の化合物は、優れた抗腫瘍効果を有することから医薬の分野において抗腫瘍剤として有用である。

【0080】

フロントページの続き

(72)発明者 大久保 満

茨城県つくば市大久保3番地 萬有製薬株式会社つくば研究所内

(72)発明者 須田 寛之

茨城県つくば市大久保3番地 萬有製薬株式会社つくば研究所内